IPF: PATHOGENESIS

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UNIVERSITÀ DEGLI STUDI DI
VERONA

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs. It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. The American Thoracic Society and European Respiratory Society (ATS/ERS), in collaboration with the American College of Chest Physicians (ACCP), published an international consensus statement in 2000 on the diagnosis and management of IPF (1). Importantly, the statement recognized IPF as a distinct clinical entity associated with the histologic appearance of usual interstitial pneumonia (UIP), and provided specific recommendations for clinicians regarding its diagnosis and management. Since the publication of the 2000

ILD classification and pathogenesis

Molecular advances

Gene Expression Profiles Distinguish Idiopathic Pulmonary Fibrosis from Hypersensitivity Pneumonitis

Moises Selman, Annie Pardo, Lourdes Barrera, Andrea Estrada, Susan R. Watson, Keith Wilson, Natasha Aziz, Naftali Kaminski*, and Albert Zlotnik*

Instituto Nacional de Enfermedades Respiratorias, Mexico City; Facultad de Ciencias, Universidad Nacional Autónoma de México, Mexico City, Mexico; Eos Biotechnology, South San Francisco, California; and Simmons Center for Interstitial Lung Disease, Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

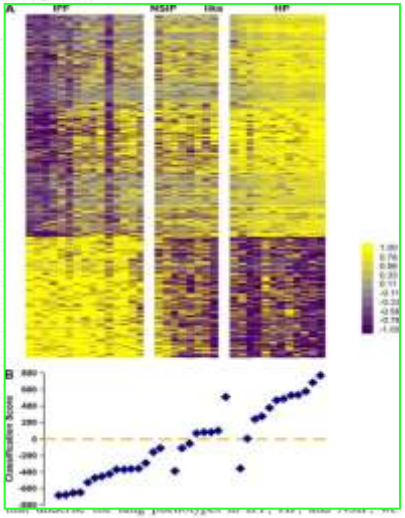
Rationale: Many of the interstitial lung diseases represent a diagnostic and therapeutic challenge because their clinical and even histologic features are often nonspecific. Likewise, the transcriptional signatures of most of them are unknown.

Objective: To compare the gene expression patterns from patients with idiopathic pulmonary fibrosis (IPF) hypersensitivity pneumonitis (HP), and nonspecific interstitial pneumonia (NSIP) using custom oligonucleotide microarrays.

Methods: We profiled lung biopsies from 15 patients with IPF, 12 with HP, and eight with NSIP. Labeled complementary ribonucleic acid was hybridized to a custom Affymetrix oligonucleotide DNA microarray using standard Affymetrix protocols. The custom array, Hu03, contained 59,619 probe sets representing an estimated 46,000 gene clusters.

Results: We identified statistically significant gene expression signatures that characterize HP and IPF. The HP gene expression signature was enriched for genes that are functionally associated with inflammation, T-cell activation, and immune responses, whereas the IPF signature was characterized by the expression of tissue remodeling, epithelial, and myofibroblast genes. We then compared these gene expression signatures to classify NSIP, a histologic pattern that is often difficult to differentiate consistently from HP and IPF. Two cases exhibited an IPF-like gene expression, another one could be more properly classified as HP, whereas others did not resemble HP or IPF, suggesting that they may represent idiopathic NSIP.

Conclusions: Our results underscore the value of gene expression signatures to classify the interstitial lung diseases and to understand pathogenic mechanisms, and suggest new ways to improve the diagnosis and treatment of patients with these diseases.

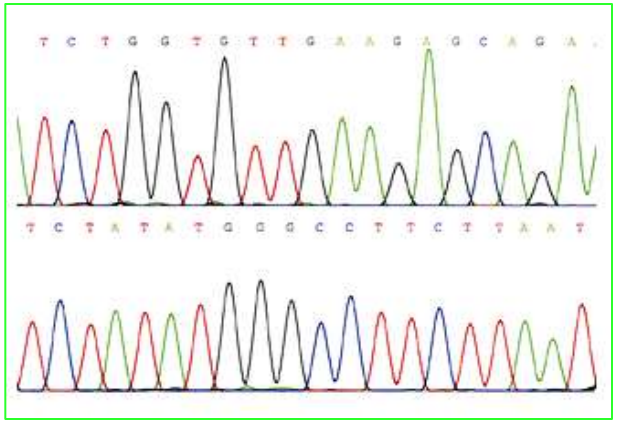


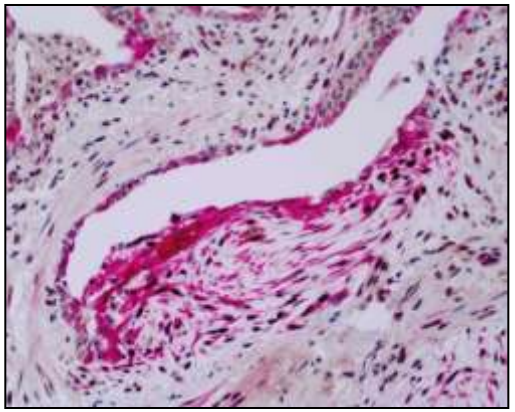
REVIEW

Beyond the diagnosis of idiopathic pulmonary fibrosis; the growing role of systems biology and stratified medicine

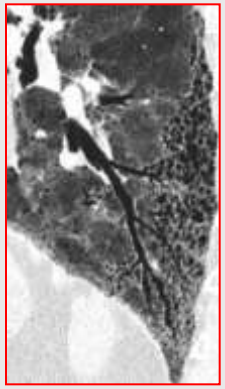
Toby M. Maher[Affil]

- Genetic analysis
- Gene expression profiling
- Molecular biology
- Molecular morphology
- Experimental studies





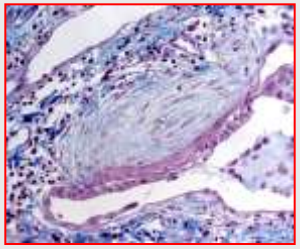
Etio-pathogenic comprehensive model for IPF: matching clinical, pathological and imaging features

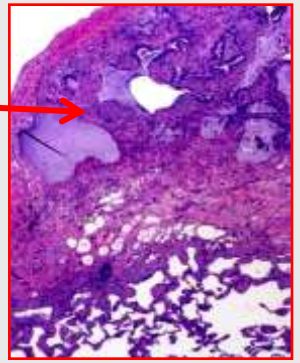


- Age
- Smoke
- Lower-posterior lobes

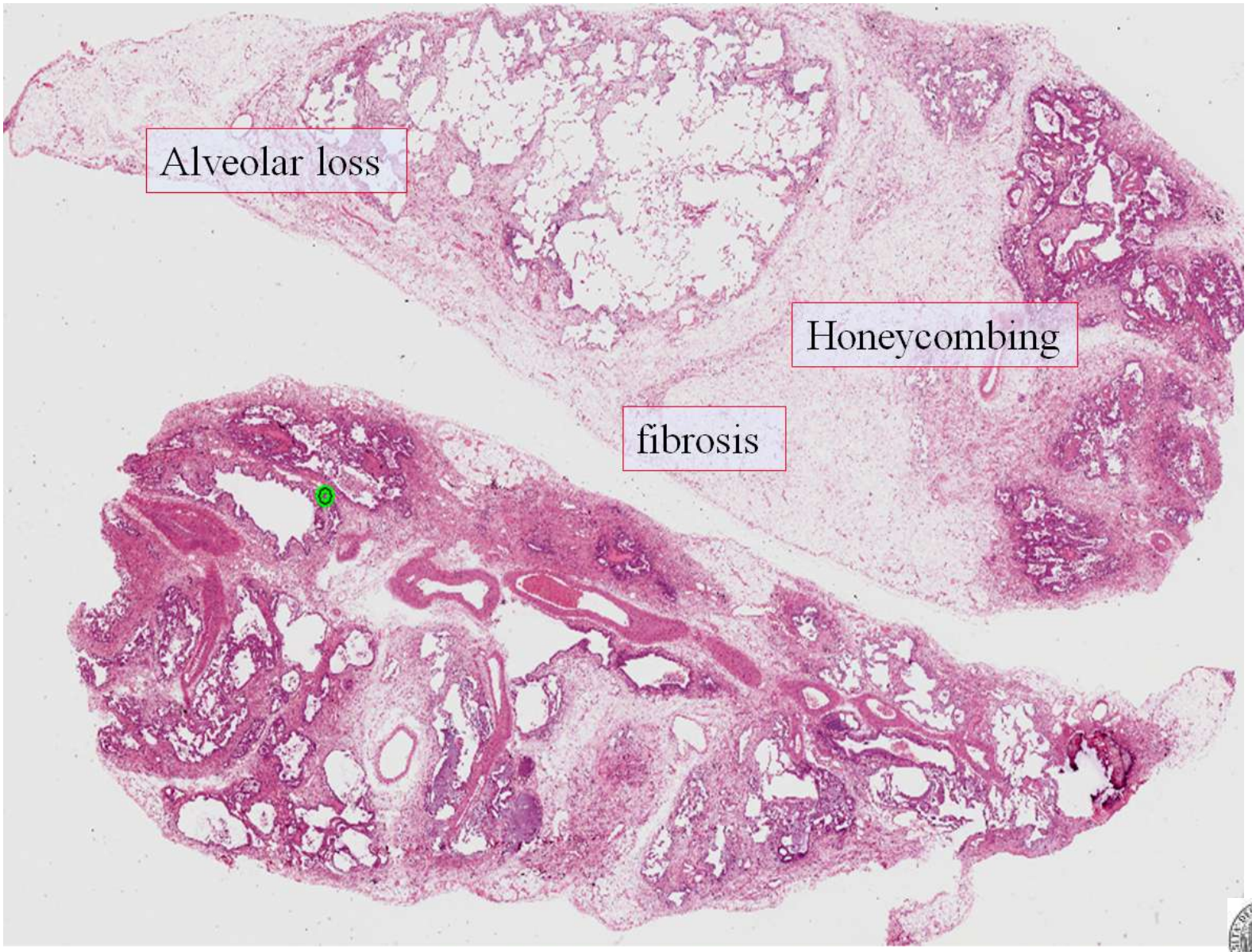
- Familial vs sporadic
- Exacerbations
- Molecular features

- Remodelling
  - *fibroblast foci*
  - *honeycombing*





What's happening here ?



IPF pathogenesis : a tragic trilogy

Ὀρέστεια

The ***Oresteia*** trilogy of Greek tragedies written by Aeschylus

1. Ἀγαμέμνων (Agamennon)
2. Χοηφόροι, *Choēphoroi* (the libation bearers)
3. Εὐμενίδες (*Eumenides)*

1. → Alveolar loss

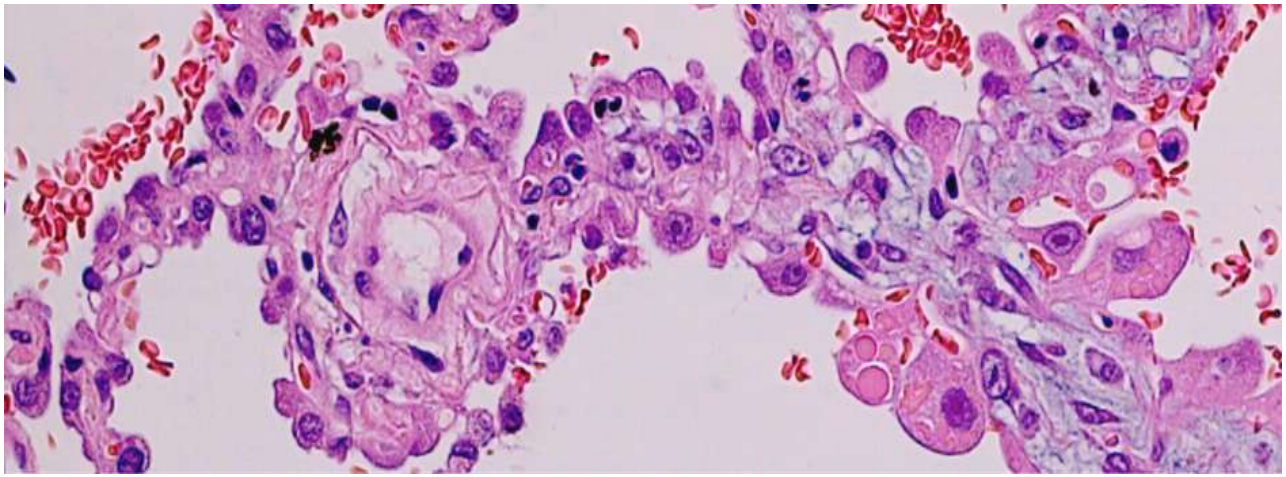
The Victim

2. → Aberrant signaling

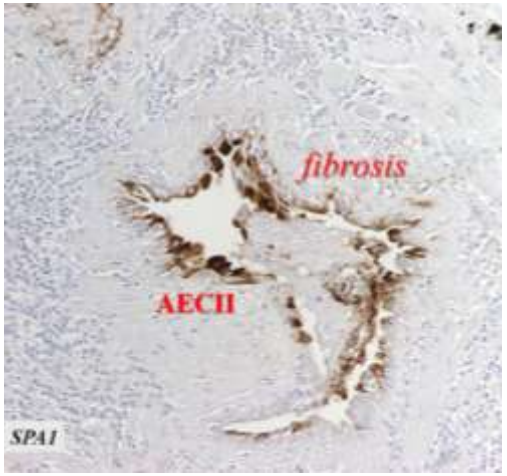
Grief and Revenge

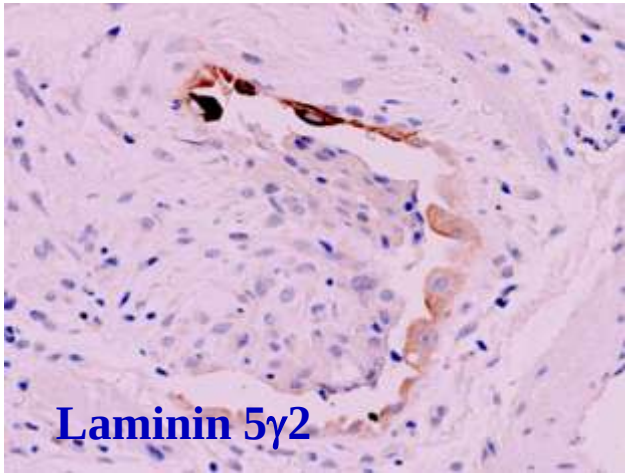
3. → Abnormal remodelling
End-stage lung

The Consequences



Pneumocyte





The Victim

Targeted Injury of Type II Alveolar Epithelial Cells Induces Pulmonary Fibrosis

Am J Respir Crit Care Med Vol 181. pp 254–263, 2010

Thomas H. Sisson[1], Michael Mendez[2], Karen Choi[1], Natalya Subbotina[1], Anthony Courey[1], Andrew Cunningham[1], Aditi Dave[1], John F. Engelhardt[3], Xiaoming Liu[3], Eric S. White[1], Victor J. Thannickal[1], Bethany B. Moore[1], Paul J. Christensen[2], and Richard H. Simon[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan Hospital, Ann Arbor; [2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Veterans Affairs Medical Center, Ann Arbor, Michigan; and [3]Department of Anatomy and Cell Biology, University of Iowa, Iowa City, Iowa

Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

VERONA, TERNI; AND FORLÌ, ITALY

Aging

Replicative senescence
and Telomere attrition

Genetic

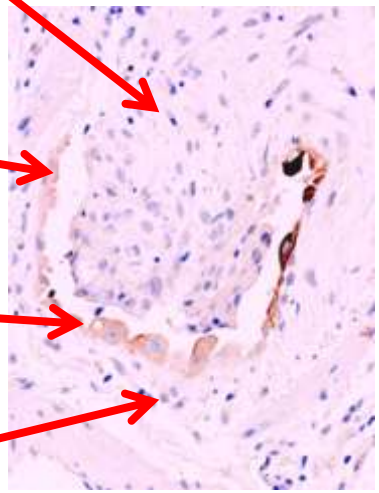
Surfactant gene mutations
Endoplasmic reticulum stress

Smoking, pollutions:

Oxidative stress, ROS, NOX4

Anatomy

Mechanical stress

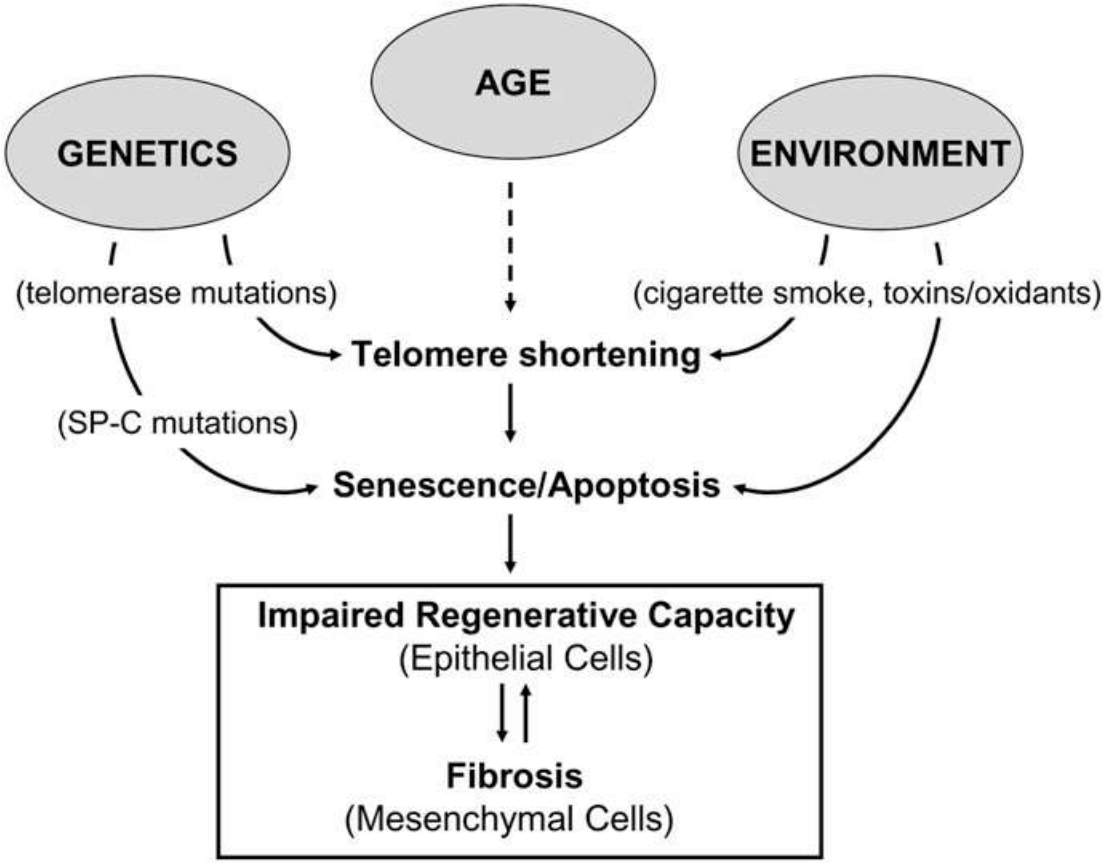


IPF

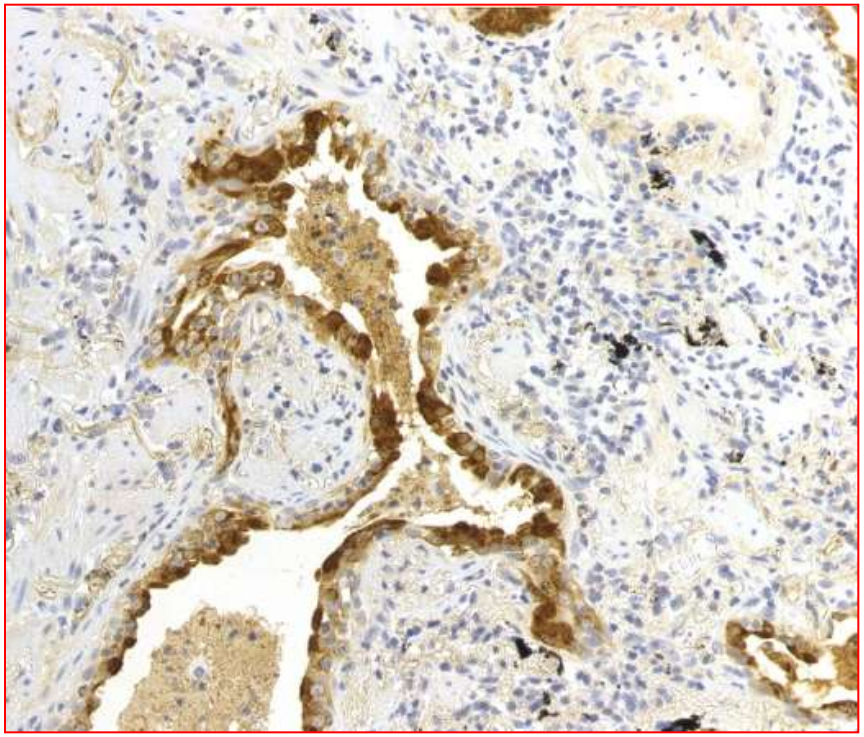
Epithelial Stem cell exhaustion

Am J Respir Crit Care Med. 2008 Oct 1;178(7):663-5. Idiopathic pulmonary fibrosis: a disorder of lung regeneration?

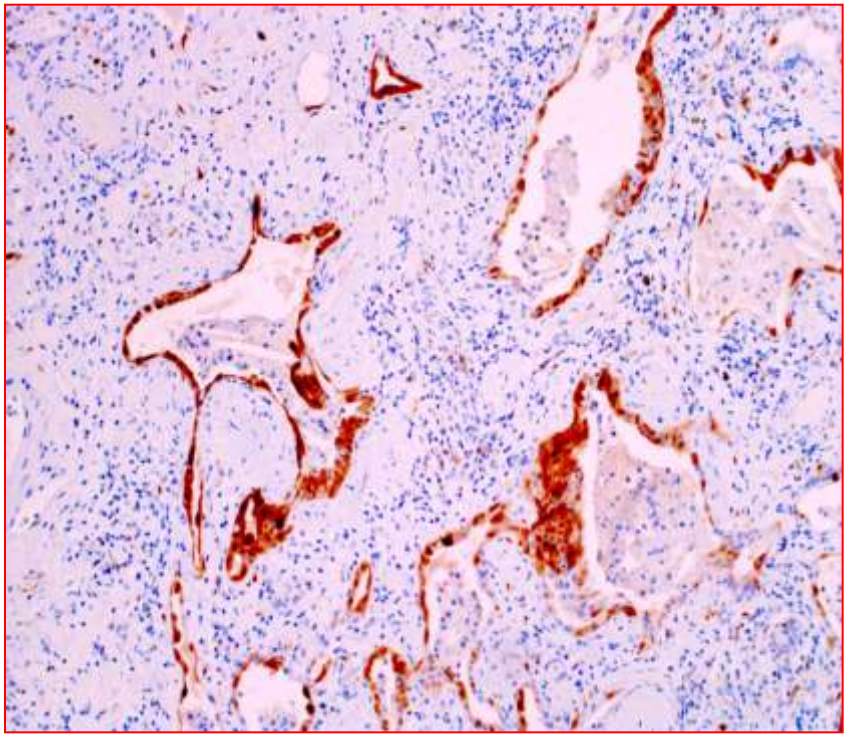
Thannickal VJ, Loyd JE.



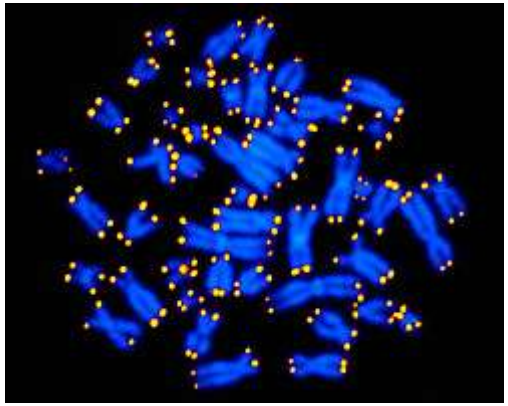
IPF
Cell senescence marker expression in AECII



Surf-Prot-A1



p16^{INK4B}



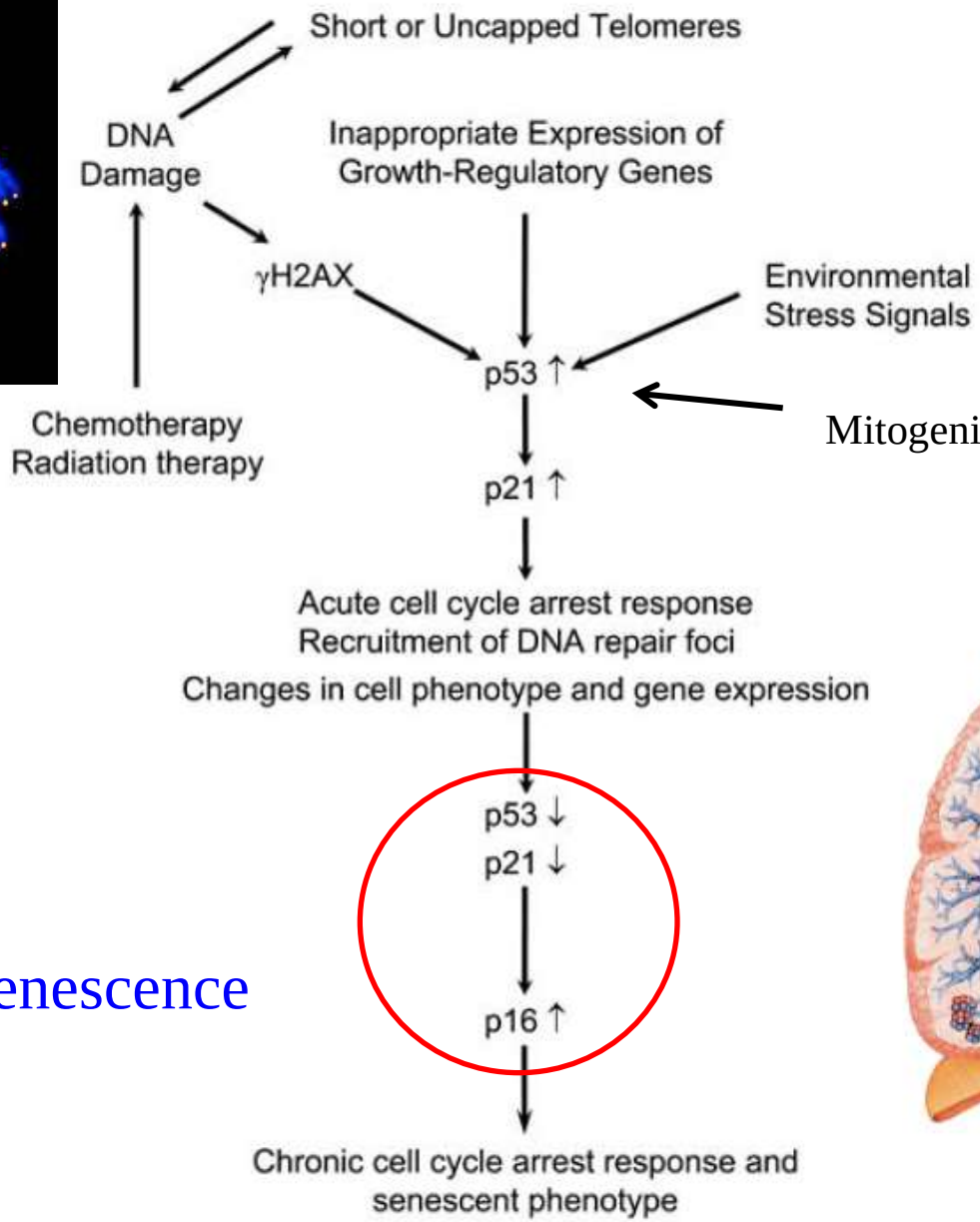
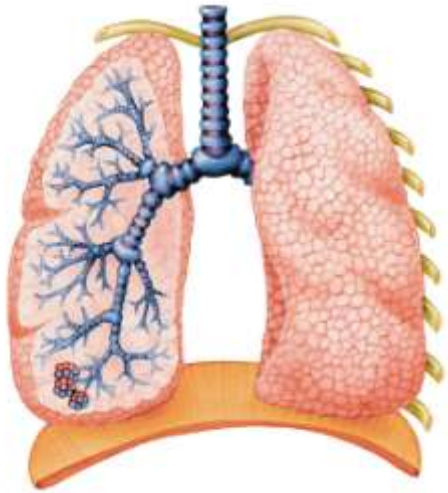


Figure 1 Induction of senescence in normal cells

Cigarette smoke



Markers of senescence

Published in final edited form as:
Am J Med Sci. 2011 June ; 341(6): 439–443. doi:10.1097/MAJ.0b013e31821a9d7a.

GENETICS IN PULMONARY FIBROSIS – FAMILIAL CASES PROVIDE CLUES TO THE PATHOGENESIS OF IPF

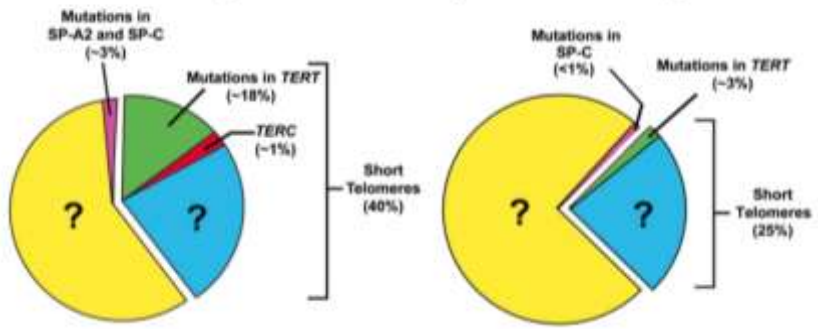
William E. Lawson, MD[1,2], **James E. Loyd, MD**[1], and **Amber L. Degryse, MD**[1]
[1]Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN

Idiopathic Pulmonary Fibrosis

Update on Genetic Discoveries

Christine Kim Garcia[1]
[1]McDermott Center for Human Genetics, University of Texas Southwestern Medical Center, Dallas, Texas

Proc Am Thorac Soc Vol 8. pp 158–162, 2011



Adult-onset pulmonary fibrosis caused by mutations in telomerase

Kalliopi D. Tsakiri*, Jennifer T. Cronkhite*, Phillip J. Kuan*, Chao Xing*†, Ganesh Raghu‡, Jonathan C. Weissler§, Randall L. Rosenblatt§, Jerry W. Shay¶, and Christine Kim Garcia*†‖

Short telomeres are a risk factor for idiopathic pulmonary fibrosis

Jonathan K. Alder*, Julian J.-L. Chen††, Lisa Lancaster‡‡, Sonye Danoff§§, Shu-chih Su‖‖, Joy D. Cogan*¶¶, Irma Vultu††, Mingyi Xie†, Xiaodong Qi†, Rubin M. Tuder††, John A. Phillips, III*¶, Peter M. Lansdorp*†††, James E. Loyd‖, and Mary Y. Armanios*¶¶

A genome-wide association study identifies an association of a common variant in *TERT* with susceptibility to idiopathic pulmonary fibrosis

T Mushiroda,[1] S Wattanapokayakit,[2] A Takahashi,[3] T Nukiwa,[4] S Kudoh,[5] T Ogura,[6] H Taniguchi,[7] M Kubo,[8] N Kamatani,[3] Y Nakamura,[1,9] the Pirfenidone Clinical Study Group[6]

J Med Genet. 2008 Oct;45(10):654-6.

IPF

Telomere dysfunction: senescence

Endoplasmic reticulum stress (unfolded proteins)

→

Epithelial stem cell exhaustion

2. Multifactorial/complex pathogenesis: genetic predisposition, cell senescence, stem cell exhaustion

- **pediatric ILD** *(Surfactant-PB or PC-deficiency, ABCA3 mutation, NKX2-1 mutations)*

- **familial IPF** *(TERT, TERC, SP-A2, SP-C, ABCA3, pro-MUC5B rs35705950 polymorphism)*
- Dyskeratosis congenita with pulmonary involvement (*telomeropathy*)

- **Idiopatic pulmonary fibrosis** - IPF/CPFE

  - genetic features: rare: *surfactant SPA2 and SPC, ABCA3 mutations,*

  frequent*: pro-MUC5B rs35705950 polymorphism,*

  - molecular features: telomere shortening, WNT-pathway activation , EMT, etc.)

Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema

MARCO CHILOSI, ANGELO CARLONI, ANDREA ROSSI, and VENERINO POLETTI

VERONA, TERNI; AND FORLÌ, ITALY

Aging

Replicative senescence
and Telomere attrition

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Smoking, pollutions:

Oxidative stress, ROS, NOX4

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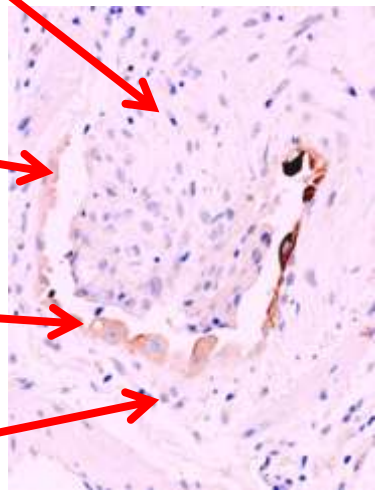
Mechanical stress



IPF

Epithelial Stem cell exhaustion

Idiopathic Pulmonary Fibrosis May Be a Disease of Recurrent, Tractional Injury to the Periphery of the Aging Lung

A Unifying Hypothesis Regarding Etiology and Pathogenesis

Kevin O. Leslie, MD

• *Context.*—Idiopathic pulmonary fibrosis is a progressive, fatal lung disease occurring in older individuals. Despite 50 years of accrued data about the disease, little progress has been made in slowing functional loss or in decreasing patient mortality.

Objective.—To present a novel hypothesis on the etiology and pathogenesis of idiopathic pulmonary fibrosis.

Design.—Published data are reviewed regarding the epidemiology, clinical presentation, natural history, radiologic findings, and pathologic findings in patients with idiopathic pulmonary fibrosis.

Results.—Patients with idiopathic pulmonary fibrosis may be predisposed genetically to tractional injury to the peripheral lung. The result is recurrent damage to the epithelial-mesenchymal interface, preferentially at the outer edges of the basilar lung lobules where tractional stress is high during inspiration, compliance is relatively low, and there is a greater tendency for alveolar collapse at end-expiration. A distinctive ''reticular network of injury'' (the *fibroblast focus*) forms, attended by a prolonged phase of wound repair (*tear and slow repair*). Discrete areas of alveolar collapse are observed in scar at the periphery of the lung lobules. The cycle repeats over many years resulting in progressive fibrous remodeling and replacement of the alveoli in a lobule by bronchiolar cysts surrounded by scar (*honeycomb lung*). Abnormalities in surfactant function are proposed as a potential mechanism of initial lung damage. Age of onset may be a function of a required threshold of environmental exposures (eg, cigarette smoking) or other comorbid injury to the aging lung.

Conclusions.—Evidence supporting this hypothesis is presented and potential mechanisms are discussed. A potential role for contributing cofactors is presented.

(*Arch Pathol Lab Med.* 2011;135:1–10; doi: 10.5858/arpa.2011-0511-OA)

J Theor Biol. 2013 Sep 7;332:136-40. doi: 10.1016/j.jtbi.2013.04.038. Epub 2013 May 9.

Heterogeneous distribution of mechanical stress in human lung: a mathematical approach to evaluate abnormal remodeling in IPF.

Carloni A[1], Poletti V, Fermo L, Bellomo N, Chilosi M

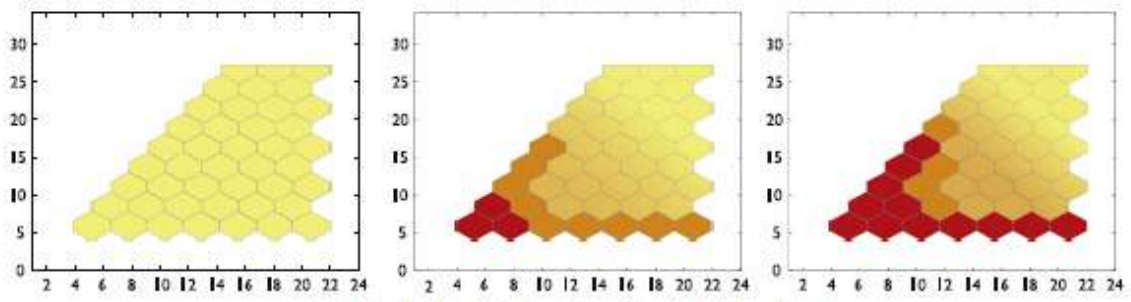
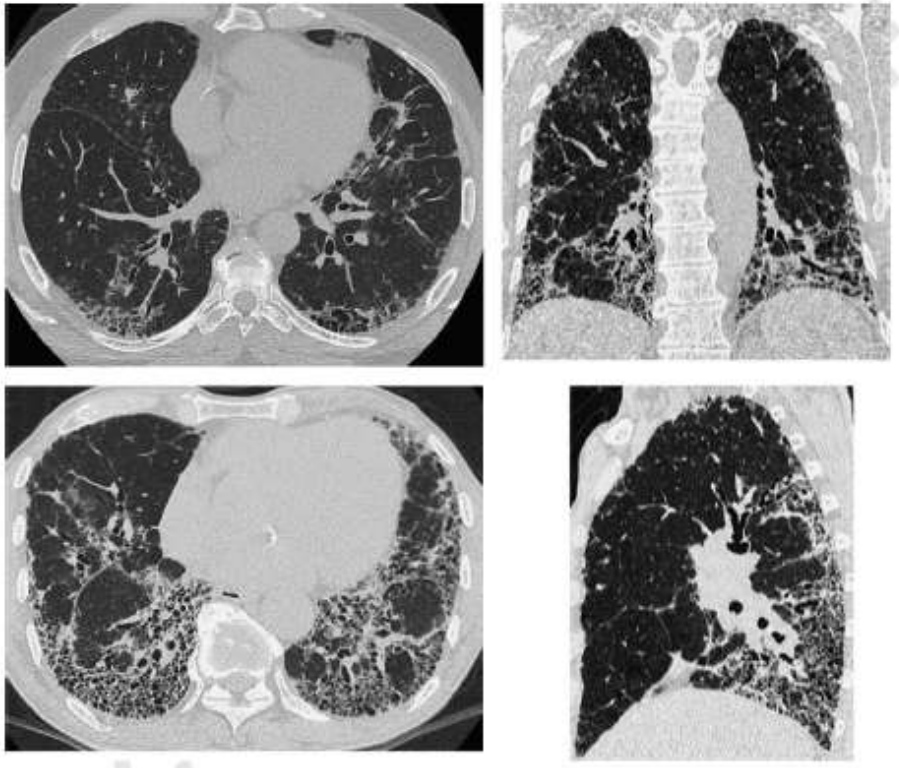


Fig. 3. Simulations of the Lung Parenchima for different times.

Maximal alveolar deformation

$$\begin{cases} \mathrm{M}\dfrac{d^2\mathrm{X}}{dt^2} = \mathrm{F}_x + \mathrm{f}_x \\ \mathrm{M}\dfrac{d^2\mathrm{Y}}{dt^2} = \mathrm{F}_y + \mathrm{f}_y \end{cases}$$



ronal and sagittal high resolution CT scan showing the typical UIP (usual interstitial pneumonitis) pattern: clustered cystic air spaces, typically of he order of 310 mm sited in the subpleural spaces, in the lower parts of the lungs (honeycomb changes).

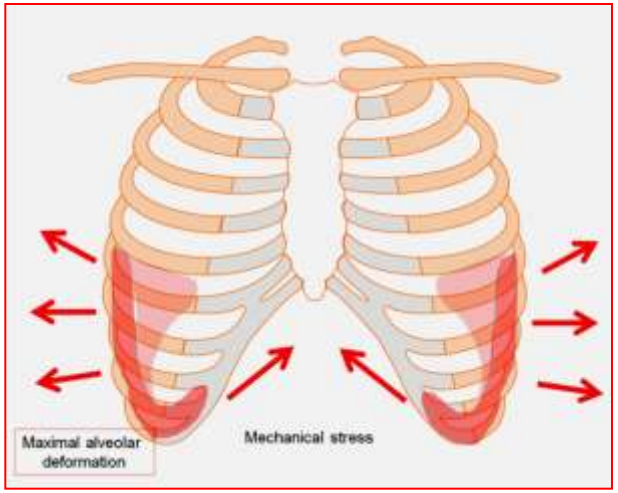
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 284, NO. 10, pp. 34607–34617, December 11, 2009

Mechanical Loading Regulates NFATc1 and β-Catenin Signaling through a GSK3β Control Node*

Received for publication, June 30, 2009, and in revised form, October 13, 2009 Published, JBC Papers in Press, October 19, 2009, DOI 10.1074/jbc.M109.039453

Buer Sen[‡1], **Maya Styner**[‡], **Zhihui Xie**[‡], **Natasha Case**[‡], **Clinton T. Rubin**[§], **and Janet Rubin**[‡]

From the [‡]*Department of Medicine, University of North Carolina, Chapel Hill, North Carolina 27599 and the* [§]*Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, New York 11794*



Mechanical stress
Mechanical cues

Cell

Role of TAZ as Mediator of Wnt Signaling

Luca Azzolin,[1,4] Francesca Zanconato,[1,4] Silvia Bresolin,[2] Mattia Forcato,[3] Giuseppe Basso,[2] Silvio Bicciato,[3] Michelangelo Cordenonsi,[1,*] and Stefano Piccolo[1,*]

[1]Department of Biomedical Sciences, University of Padua School of Medicine, viale Colombo 3, 35126 Padua, Italy
[2]Department of Woman and Child Health, University of Padova, via Giustiniani 3, 35128 Padova, Italy
[3]Center for Genome Research, Department of Biomedical Sciences, University of Modena and Reggio Emilia, via G. Campi 287, 41100 Modena, Italy
[4]These authors contributed equally to this work
*Correspondence: michelangelo.cordenonsi@unipd.it (M.C.), piccolo@bio.unipd.it (S.P.)
http://dx.doi.org/10.1016/j.cell.2012.11.027

WNT-β-catenin
TAZ

ARTICLE

doi:10.1038/nature10137

Role of YAP/TAZ in mechanotransduction

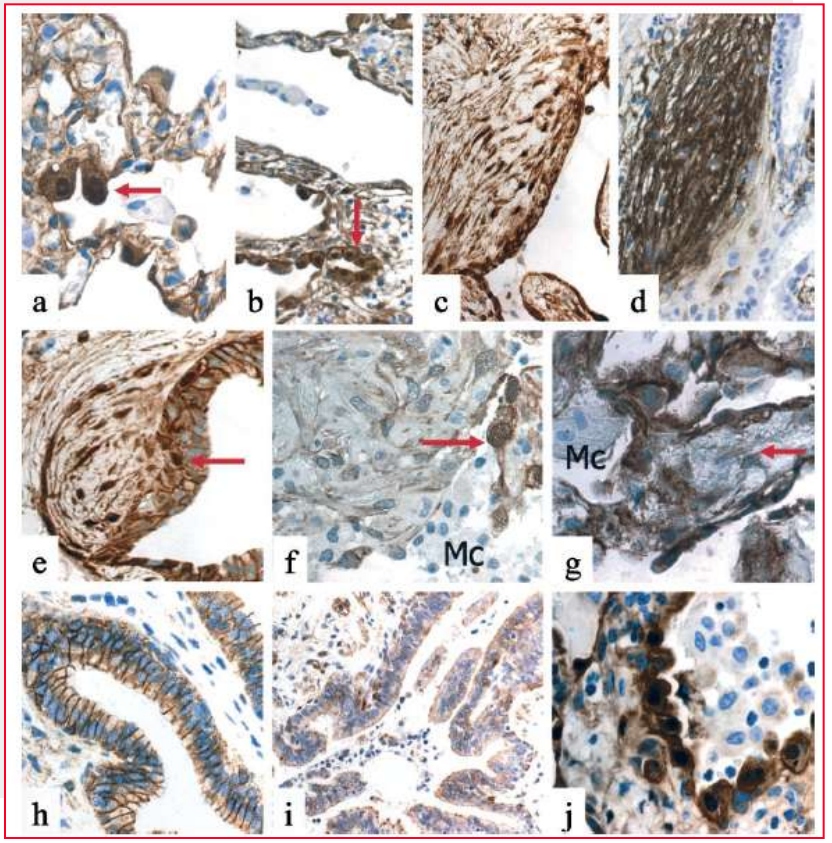
Sirio Dupont[1]*, Leonardo Morsut[1]*, Mariaceleste Aragona[1], Elena Enzo[1], Stefano Giulitti[2], Michelangelo Cordenonsi[1], Francesca Zanconato[1], Jimmy Le Digabel[3], Mattia Forcato[4], Silvio Bicciato[4], Nicola Elvassore[2] & Stefano Piccolo[1]

American Journal of Pathology, Vol. 162, No. 5, May 2003

Aberrant Wnt/β-Catenin Pathway Activation in Idiopathic Pulmonary Fibrosis

Marco Chilosi,* Venerino Poletti,† Alberto Zamò,* Maurizio Lestani,* Licia Montagna,* Paola Piccoli,* Serena Pedron,* Manuela Bertaso,* Aldo Scarpa,* Bruno Murer,‡ Alessandra Cancellieri,§ Roberta Maestro,¶ Gianpietro Semenzato,‖ and Claudio Doglioni**

From the Department of Pathology, University of Verona, Verona; the Department of Pneumology,† Forlì City Hospital, Forlì; the Department of Pathology,‡ Mestre City Hospital, Mestre; the Department of Pathology,§ Maggiore Hospital, Bologna; the Department of Experimental Oncology,¶ Centro di Riferimento Oncologico Aviano National Cancer Institute, Aviano; the Department of Clinical and Experimental Medicine,‖ University of Padua, Padua; and the Department of Pathology,** Belluno City Hospital, Belluno, Italy*



Chilosi et al. Am J Pathol ;162: May 2003

OPEN ACCESS Freely available online

PLoS One. 2008 May 14;3(5):e2142

PLoS one

Functional Wnt Signaling Is Increased in Idiopathic Pulmonary Fibrosis

Melanie Königshoff, Nisha Balsara, Eva-Maria Pfaff, Monika Kramer, Izabella Chrobak, Werner Seeger, Oliver Eickelberg*

Department of Medicine, University of Giessen Lung Center, University of Giessen, Giessen, Germany

J Clin Invest 2009;119:772–787.

Research article

WNT1-inducible signaling protein–1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis

Melanie Königshoff,[1] Monika Kramer,[1] Nisha Balsara,[1] Jochen Wilhelm,[1] Oana Veronica Amarie,[1] Andreas Jahn,[1] Frank Rose,[2] Ludger Fink,[1] Werner Seeger,[1] Liliana Schaefer,[3] Andreas Günther,[1] and Oliver Eickelberg[4]

WNT up-regulation in IPF

Proc Natl Acad Sci U S A. 2010 Aug 10;107(32):14309-14

Inhibition of Wnt/β-catenin/CREB binding protein (CBP) signaling reverses pulmonary fibrosis

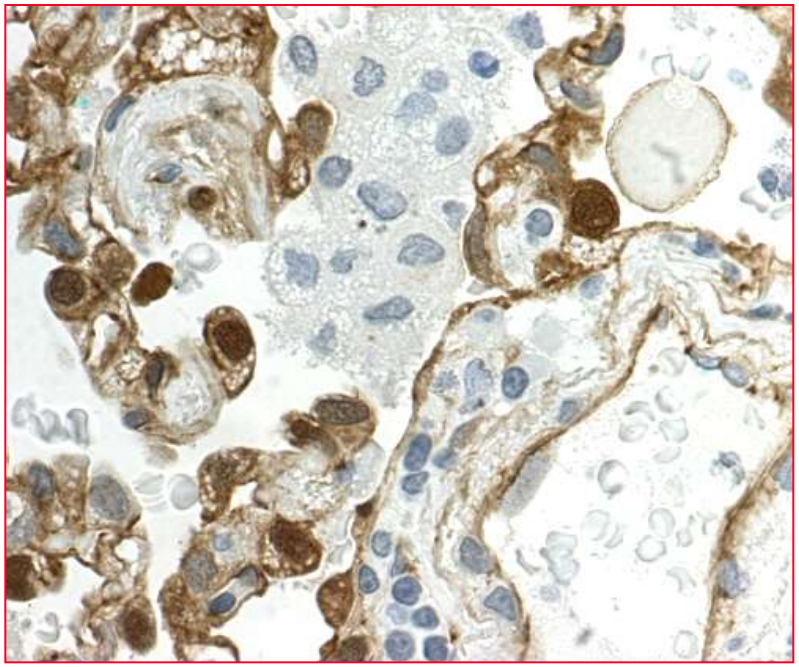
William R. Henderson, Jr.[a,1], Emil Y. Chi[b], Xin Ye[a], Cu Nguyen[c], Ying-tzang Tien[b], Beiyun Zhou[d], Zea Borok[d,e], Darryl A. Knight[f], and Michael Kahn[c,e,1]

Am J Respir Crit Care Med. 2014 Jun 12. [Epub ahead of print]

Wnt Co-receptor Lrp5 is a Driver of Idiopathic Pulmonary Fibrosis.

Lam AP[1], Herazo-Maya JD, Sennello JA, Flozak AS, Russell S, Mutlu GM, Budinger GR, DasGupta R, Varga J, Kaminski N, Gottardi CJ.

b-catenin nuclear accumulation in type-II pneumocytes



WNT-pathway

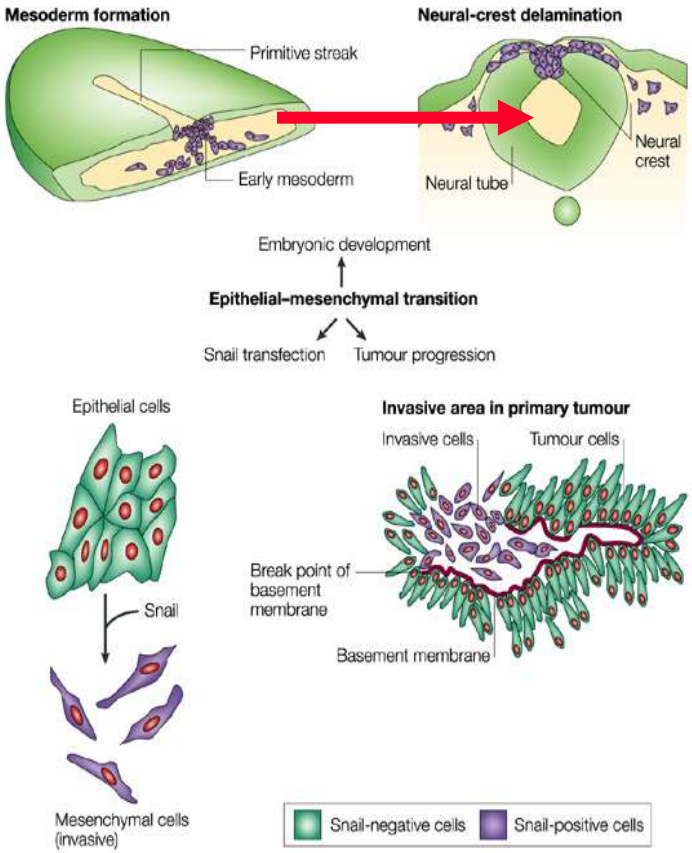
β-catenin → • Cyclin-D1 • MMP7 • *c-myc* → Proliferation Apoptosis

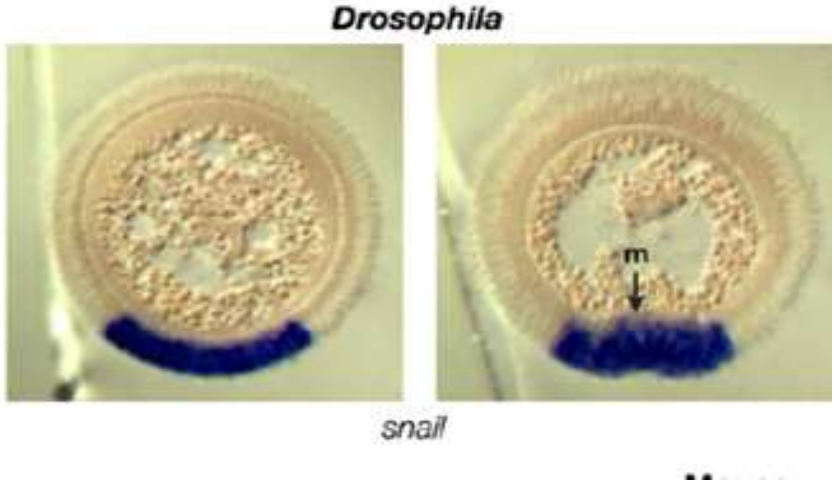
EMT

J Biol Chem. 2003 Oct 10;278(41):40231-8.

β-Catenin is required for specification of proximal/distal cell fate during lung morphogenesis. *Mucenski ML, Wert SE, Nation JM, Loudy DE, Huelsken J, Birchmeier W, Morrisey EE, Whitsett JA.* Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229-3039, USA.

EMT and embriogenesis





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PLoS GENETICS

Dual Functions of ASCIZ in the DNA Base Damage Response and Pulmonary Organogenesis

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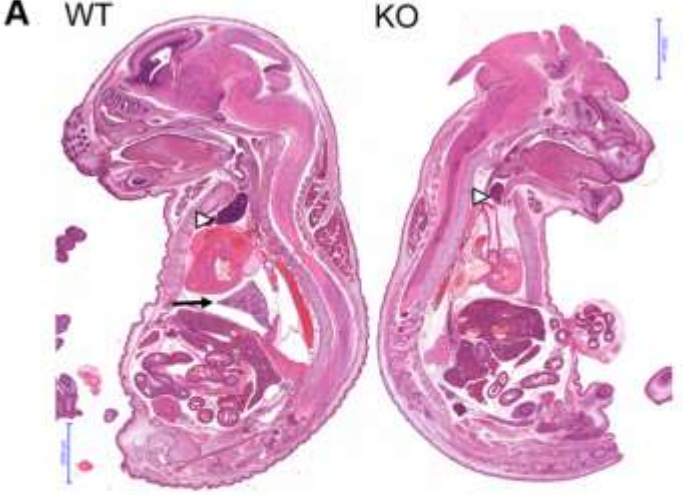
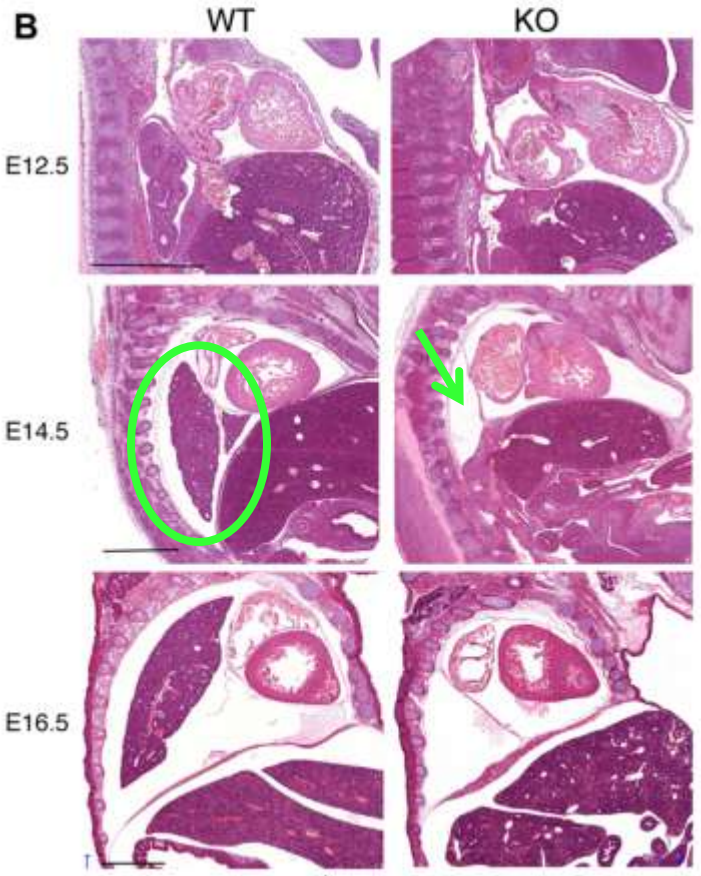
1 St. Vincent's Institute of Medical Research, Fitzroy, Australia, 2 Department of Medicine, St. Vincent's Hospital, The University of Melbourne, Fitzroy, Australia, 3 Department of Biochemistry and Molecular Biology and Department of Anatomy and Developmental Biology, Monash University, Clayton, Australia, 4 Queensland Institute of Medical Research, Herston, Australia, 5 Department of Radiation Genetics, Graduate School of Medicine, Kyoto University, Kyoto, Japan, 6 Cancer Research Institute, Kanazawa University, Ishikawa, Japan, 7 Central Clinical Division, University of Queensland, Royal Brisbane Hospital, Herston, Australia

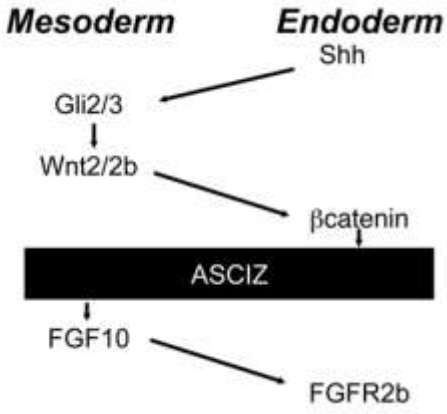
Abstract

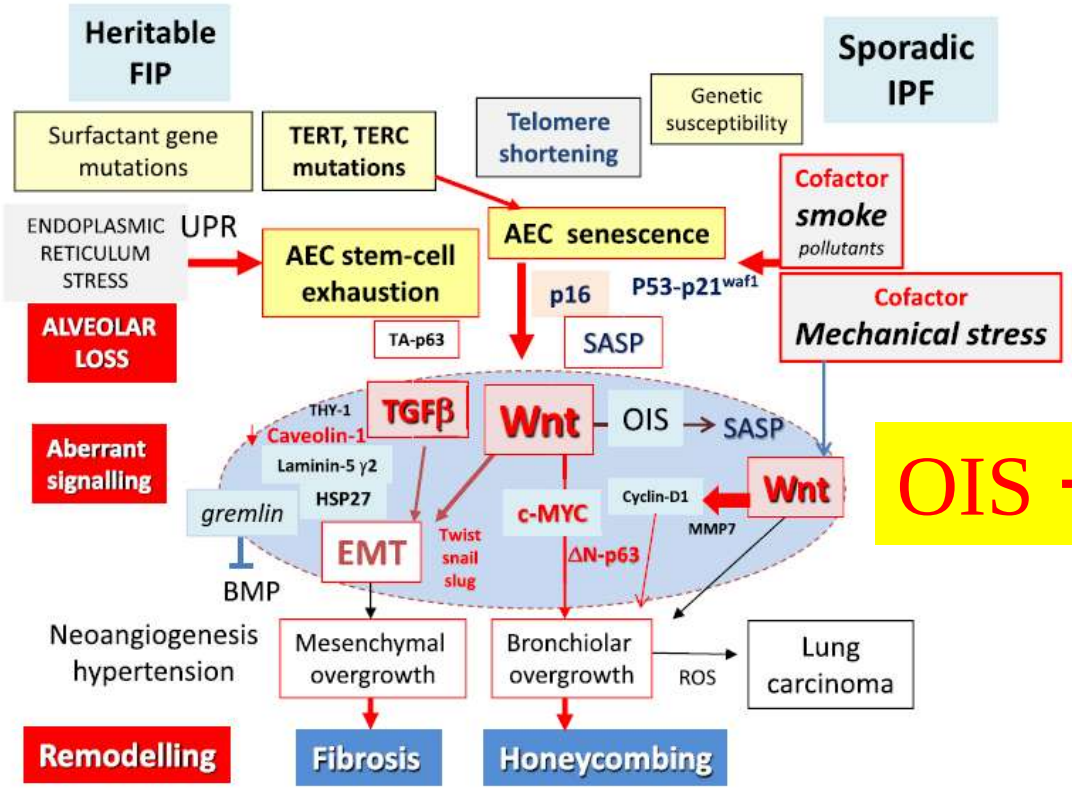
Zn^{2+}-finger proteins comprise one of the largest protein superfamilies with diverse biological functions. The ATM substrate Chk2-interacting Zn^{2+}-finger protein (ASCIZ; also known as ATMIN and ZNF822) was originally linked to functions in the DNA base damage response and has also been proposed to be an essential cofactor of the ATM kinase. Here we show that absence of ASCIZ leads to *p53*-independent late-embryonic lethality in mice. *Asciz*-deficient primary fibroblasts exhibit increased sensitivity to DNA base damaging agents MMS and H_2O_2, but *Asciz* deletion or knock-down does not affect ATM levels and activation in mouse, chicken, or human cells. Unexpectedly, *Asciz*-deficient embryos also exhibit severe respiratory tract defects with complete pulmonary agenesis and severe tracheal atresia. Nkx2.1-expressing respiratory precursors are still specified in the absence of ASCIZ, but fail to segregate properly within the ventral foregut, and as a consequence lung buds never form and separation of the trachea from the oesophagus stalls early. Comparison of phenotypes suggests that ASCIZ functions between Wnt2-2b/ß-catenin and FGF10/FGF-receptor 2b signaling pathways in the mesodermal/endodermal crosstalk regulating early respiratory development. We also find that ASCIZ can activate expression of reporter genes via its SQ/TQ-cluster domain *in vitro*, suggesting that it may exert its developmental functions as a transcription factor. Altogether, the data indicate that, in addition to its role in the DNA base damage response, ASCIZ has separate developmental functions as an essential regulator of respiratory organogenesis.





	lung	trachea	oesophagus
Gli 2/3	-	-	-
Wnt 2/2b	-	-	+
Shh-Cre βcatenin	-	-	+
ASCIZ	-	(+)	+
FGF10	-	+	+
FGFR2b	-	+	+





OIS → SASP

Fig 8. General scheme describing the different steps of idiopathic pulmonary fibrosis pathogenesis as proposed in this review.

Oreste

Grief and Revenge

- beta-catenin is an oncogene
- can trigger cell senescence by OIS,
- can amplify in a vicious circle aberrant signaling and SASP

MOLECULAR AND CELLULAR BIOLOGY, Mar. 2008, p. 1713–1723 Vol. 28, No. 5
0270-7306/08/$08.00+0 doi:10.1128/MCB.01360-07

β-Catenin Expression Results in p53-Independent DNA Damage and Oncogene-Induced Senescence in Prelymphomagenic Thymocytes In Vivo▽†

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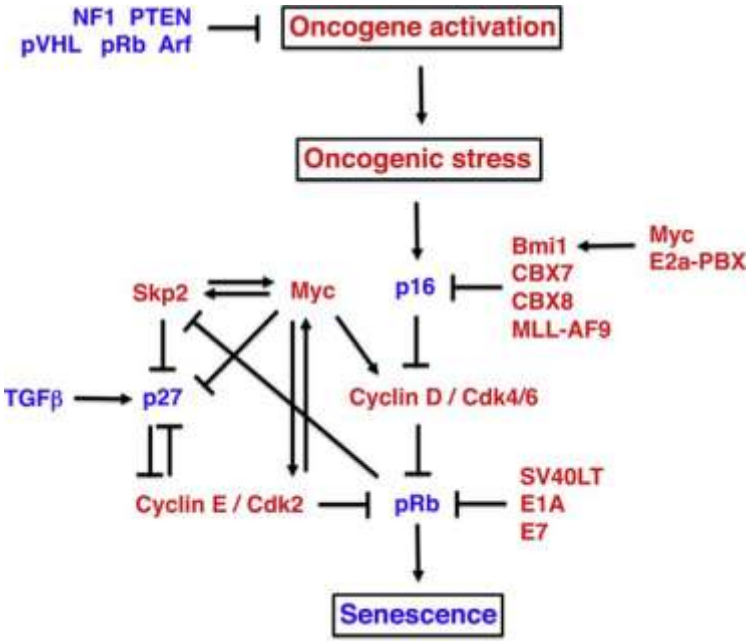

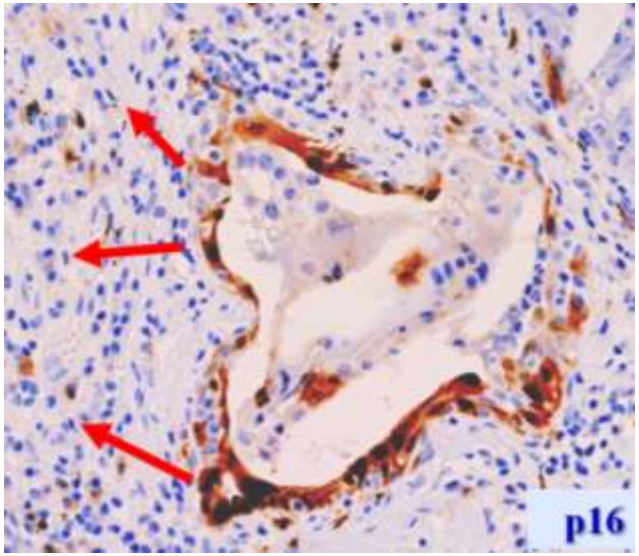

SASP

Oncogene (2012), 1–9

www.nature.com/onc

ORIGINAL ARTICLE

Molecular basis for the tissue specificity of β-catenin oncogenesis

A Sharma and JM Sen

The Senescence-Associated Secretory Phenotype: The Dark Side of Tumor Suppression

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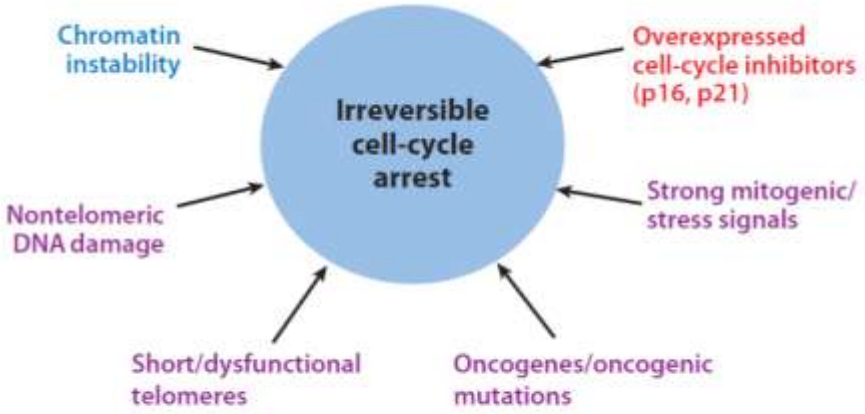

DNA damage = SASP

No DNA damage = No SASP

Table 1 The senescence-associated secretory phenotype (SASP). Factors significantly altered between presenescent and senescent states are listed

SASP factors[a]	Secretory profile of senescent cells[b]	Changes in the SASP due to the loss of p53 and/or gain of oncogenic RAS
Soluble factors		
Interleukins (IL)		
IL-6	↑	↑
IL-7	↑	↑
IL-1a, -1b	↑	↑
IL-13	↑	↑
IL-15	↑	↑
Chemokines (CXCL, CCL)		
IL-8	↑	↑
GRO-a,-b,-g[c]	↑	↑
MCP-2	↑	↑
MCP-4	↑	×
MIP-1a	↑	↑
MIP-3a	↑	×
HCC-4	↑	×
Eotaxin	×	↑
Eotaxin-3	↑	↑
TECK	×	↑
ENA-78	×	↑
I-309	×	↑
I-TAC	×	↓
Other inflammatory factors		
GM-CSF	↑	↑
G-CSF	×	↑
IFN-γ	×	↑
BLC	×	↑
MIF	↑	↓
Growth factors and regulators		
Amphiregulin	↑	×
Epiregulin	↑	×
Heregulin	↑	×
EGF	↑ or ×	↑
bFGF	↑	↑
HGF	↑	×
KGF (FGF7)	↑	↑
VEGF	↑	×
Angiogenin	↑	×
SCF	↑	×
SDF-1	↑ or ×	↑
PIGF	↑	×
NGF	×	↓

(*Continued*)

The secretory phenotype of senescent cells

Am J Respir Cell Mol Biol. 2013 Mar 22. [Epub ahead of print]

WNT/β-Catenin Signaling Induces Interleukin 1β Expression by Alveolar Epithelial Cells in Pulmonary Fibrosis.

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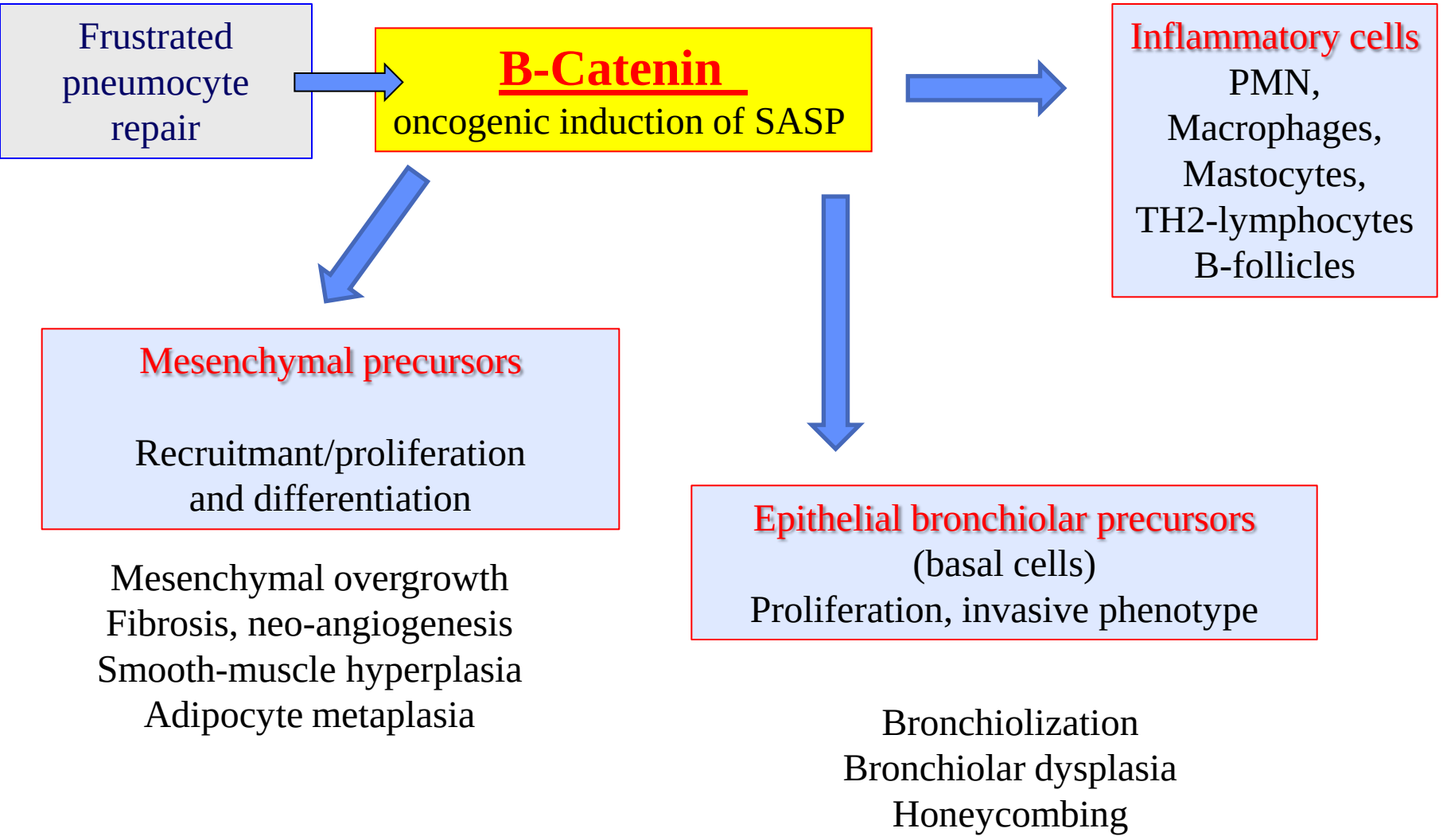
Abstract

Idiopathic pulmonary fibrosis (IPF) is a lethal lung disease of yet unknown etiology. It is characterised by alterations of the alveolar epithelium, myofibroblast activation, and increased extracellular matrix deposition. Recently, reactivation of WNT/β-catenin signaling has been linked with IPF. The cell-specific mechanisms and mediators of WNT/β-catenin signaling in the lung, however, remain elusive. Here, we applied an unbiased gene expression screen to identify epithelial cell-specific mediators of WNT/β-catenin signaling. We found the proinflammatory cytokine interleukin (IL) 1β as one of the most upregulated genes in primary murine alveolar epithelial type (AT) II cells after WNT3a treatment. Increased transcript and protein expression of IL-1β upon WNT3a treatment was further detected in primary ATII cells by qRT-PCR (log-fold change: 2.0 +/- 0.5) and ELISA (1.8 fold increase). We observed significant IL-1β and IL-6 upregulation in bronchoalveolar lavage fluid (BALF) in bleomycin induced lung fibrosis in vivo. Importantly, primary fibrotic ATII cells secreted enhanced IL-1β and IL-6 in vitro. Furthermore, orotracheal application of recombinant WNT protein in TOPGAL reporter animals led to WNT/β-catenin activation in epithelial cells along with a significant increase in IL-1β and IL-6 in vivo (2.7-fold and 6.0-fold, respectively). Finally, we found increased WNT3a protein in fibrotic alveolar epithelium accompanied by enhanced IL-1β and IL-6 level in BALF from IPF patients. Taken together, our findings revealed that the alveolar epithelium is a relevant source of proinflammatory cytokines induced by active WNT/β-catenin. Thus, WNT/interleukin signaling represents a novel link between developmental pathway reactivation and inflammation in the development of pulmonary fibrosis.

PMID: 23526221 [PubMed - as supplied by publisher]

OIS and SASP in IPF

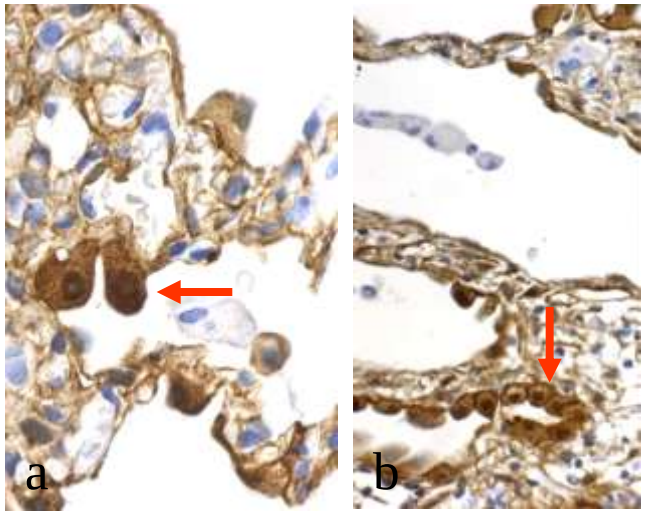


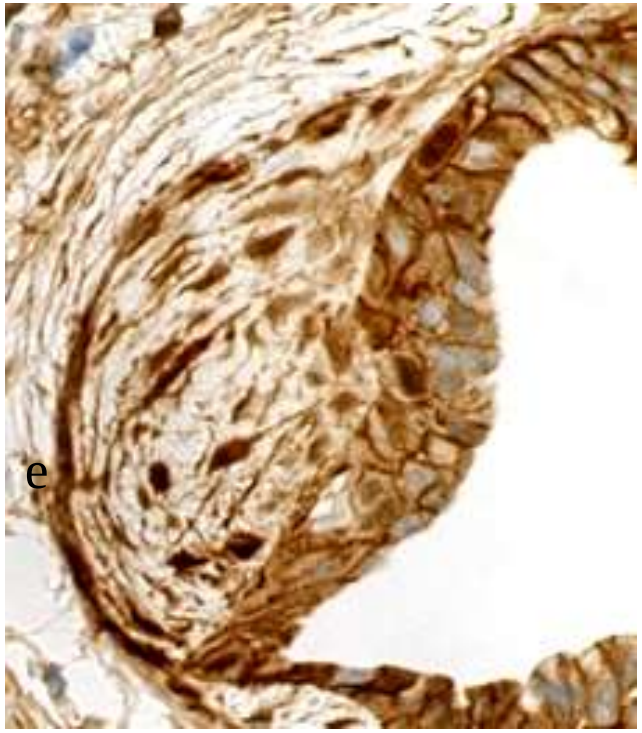
Alveolar Structures

Cells expressing nuclear β-catenin were found lining damaged alveolar structures, recognized as cuboidal type II pneumocytes by morphology and immunophenotype on serial sections (surfactant-A-positive and ΔN-p63-negative). The number of positive cuboidal pneumocytes progressively increased from normal to severely affected alveoli (Figure 2, a and b). β-catenin nuclear expression was observed in all enlarged and/or atypical cuboidal cells.

Fibroblast Foci

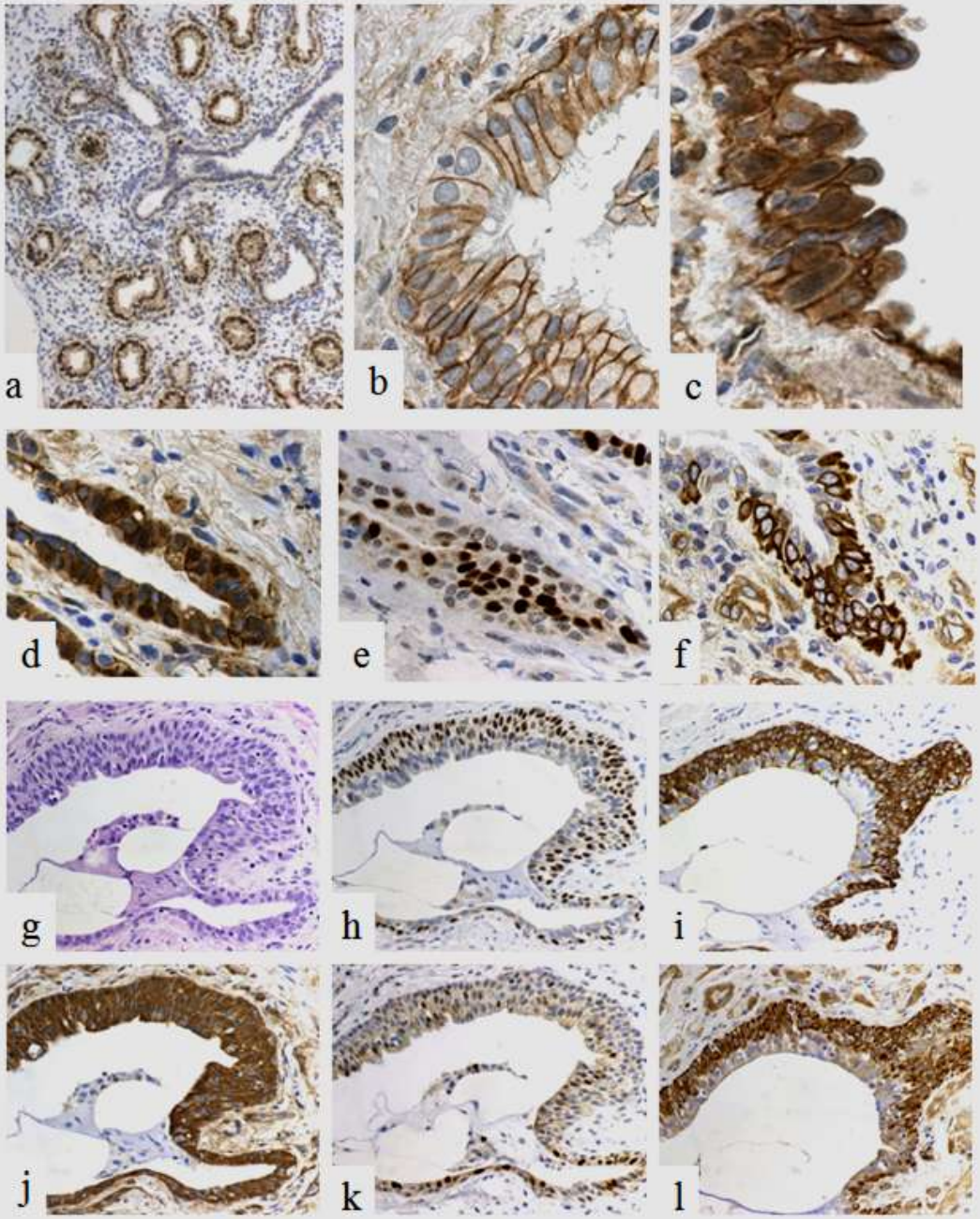
Nuclear expression of β-catenin was observed in spindle cells forming fibroblast foci present in 16 of 20 samples in which these lesions could be clearly identified and immunohistochemically analyzed on serial sections (Figure 2, c and e). These foci, characterized as myofibroblastic by intense α-smooth muscle actin and tenascin immunoreactivity on serial sections (Figure 2d), were frequently intramural and located under abnormal bronchiolar segments, as forming strictly related lesions (Figure 2e). This pattern was different from that observed in intra-alveolar inflammatory polyps (Masson's bodies) present in OP/BOOP (Figure 2f) and interstitial fibroblasts of AIP/DAD (Figure 2g) samples used as control, in which only a minority (less than 10%) of spindle cells expressed nuclear β-catenin.





Chilosi et al. Am J Pathol ;162: May 2003

Figure 1



IPF

- nuclear expression of beta-Catenin in proliferative bronchiolar lesions and honeycoming.

- abnormal expression of WNT-target proteins
(MMP7, cyclin-D1)
in bronchiolar basal cells

Bronchiolar Lesions

A striking number of epithelial cells expressing β-catenin nuclear accumulation were demonstrated in proliferative bronchiolar lesions in most (18 of 20) samples (Figure 1; c, d, and j). Nuclear β-catenin accumulation was heterogeneously distributed in these abnormal structures, mainly occurring in clusters of hyperplastic basal cells. The presence of nuclear β-catenin was particularly evident in bronchioles exhibiting honeycomb modifications (Figure 1, g and l) and/or bronchiolization (a process of migrating bronchiolar cells progressively colonizing alveolar spaces). Interestingly, at the same sites nuclear overexpression of p53 and $p21^{waf1}$ could be demonstrated as previously described.[16] The bronchiolar nature of all these lesions was confirmed on serial sections by the use of antibodies recognizing ΔN-p63 and high-molecular weight cytokeratin CK5 (Figure 1, h and i), and by the absence of both surfactant-A and CC10 antigens as previously demonstrated.[16]

Chilosi et al. Am J Pathol ;162: May 2003

REVIEW

Cancer Biology & Therapy 10:3, 219-222; August 1, 2010; © 2010 Landes Bioscience

The role of the miR-200 family in epithelial-mesenchymal transition

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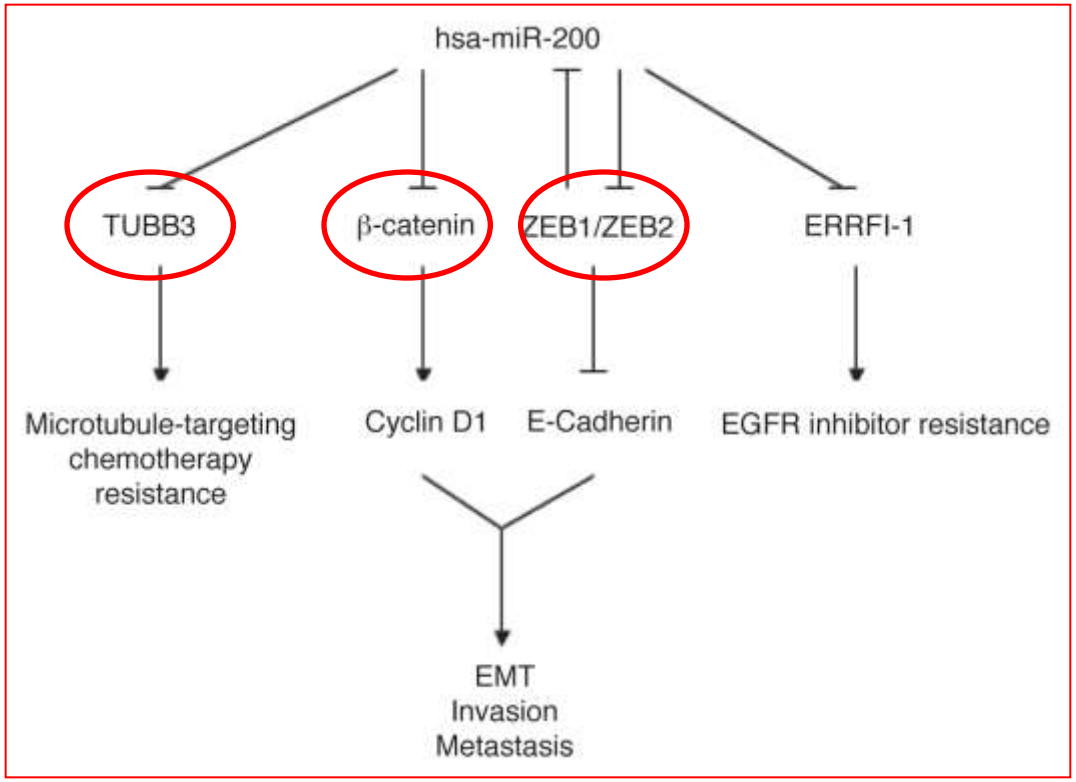
Key words: miRNAs, mir-200, epithelial-mesenchymal transition, β-catenin/Wnt signaling, microenvironment, metastasis, RNA

Abbreviations: miRNAs, microRNAs; EMT, epithelial-to-mesenchymal transition; ERRFI-1, ErbB receptor inhibitor-1; TUBB3, class III β-tubulin; TGFβ, transforming growth factor beta

MicroRNAs (miRNAs) are single-stranded, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Genes encoding miRNAs are located in regions of the genome that are commonly amplified, deleted or rearranged. They are commonly dysregulated in human cancers and known to act as oncogenes or tumor suppressors. Members of the miR-200 miRNA family are downregulated in human cancer cells and tumors due to aberrant epigenetic gene silencing and play a critical role in the suppression of epithelial-to-mesenchymal transition (EMT), tumor cell adhesion, migration, invasion and metastasis, by targeting and repressing the expression of key mRNAs that are involved in EMT (*ZEB1 and ZEB2*), β-catenin/Wnt signaling *(β-catenin*), EGFR inhibitor resistance (*ERRFI-1*) and chemoresistance to therapeutic agents (*TUBB3*). Since the miR-200 family functions as putative tumor suppressors and represent biomarkers for poorly differentiated and aggressive cancers, restoration of miR-200 expression may have therapeutic implications for the treatment of metastatic and drug-resistant tumors.



The American Journal of Pathology, Vol. 180, No. 2, February 2012

DOI: 10.1016/j.ajpath.2011.10.005

Cardiovascular, Pulmonary, and Renal Pathology

Participation of miR-200 in Pulmonary Fibrosis

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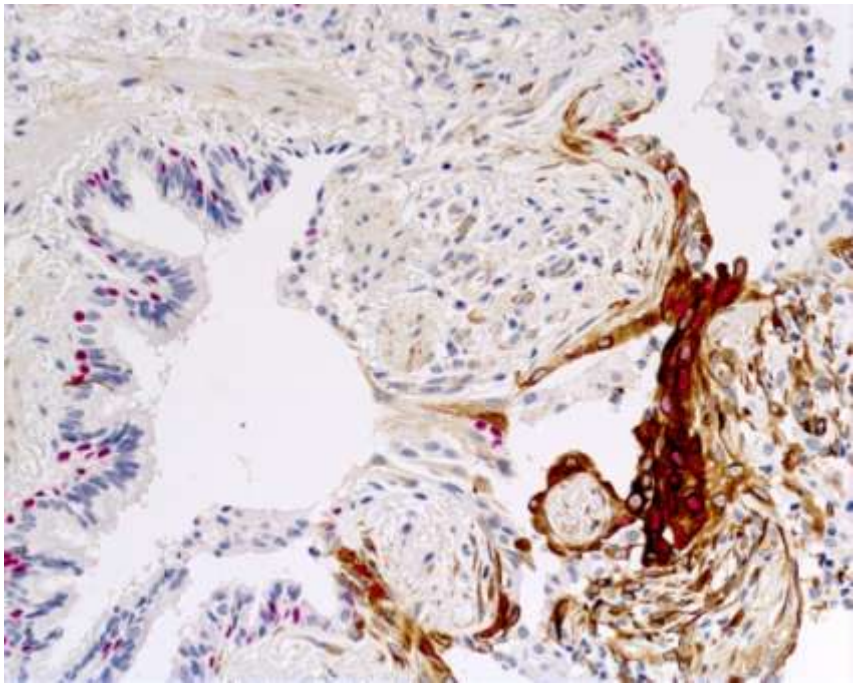
Excessive extracellular matrix production by fibroblasts in response to tissue injury contributes to fibrotic diseases, such as idiopathic pulmonary fibrosis (IPF). Epithelial-mesenchymal transition, involving transition of alveolar epithelial cells (AECs) to pulmonary fibroblasts, appears to be an important contributory process to lung fibrosis. Although aberrant expression of microRNAs (miRs) is involved in a variety of pathophysiologic processes, the role of miRs in fibrotic lung diseases is less well understood. In the present study, we found that miR-200a, miR-200b, and miR-200c are significantly down-regulated in the lungs of mice with experimental lung fibrosis. Levels of miR-200a and miR-200c were reduced in the lungs of patients with IPF. miR-200 had greater expression in AECs than in lung fibroblasts, and AECs from mice with experimental pulmonary fibrosis had diminished expression of miR-200. We found that the miR-200 family members inhibit transforming growth factor-β1–induced epithelial-mesenchymal transition of AECs. miR-200 family members can reverse the fibrogenic activity of pulmonary fibroblasts from mice with experimental pulmonary fibrosis and from patients with IPF. Indeed, the introduction of miR-200c diminishes experimental pulmonary fibrosis in mice. Thus, the miR-200 family members participate importantly in fibrotic lung diseases and suggest that restoring miR-200 expression in the lungs may represent a novel therapeutic approach in treating pulmonary fibrotic diseases. *(Am J Pathol 2012, 180:484–493; DOI: 10.1016/j.ajpath.2011.10.005)*

Table 1 | Validated targets of miR-200 family members

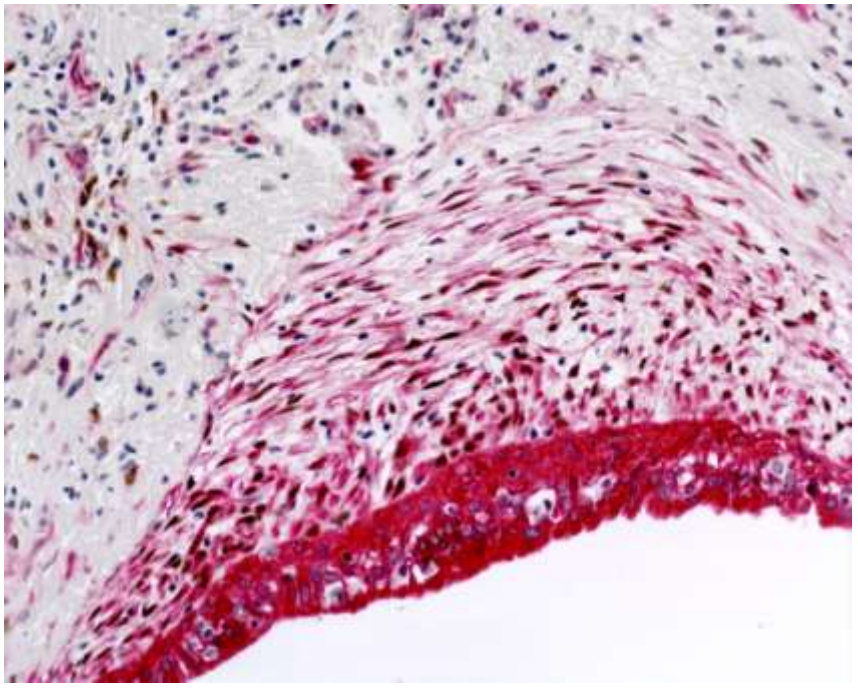
Target	miR-200 member	References
ZEB1	All family members	Hurteau *et al*, 2007; Gregory *et al*, 2008a; Park *et al*, 2008; Burk *et al*, 2008; Korpal *et al*, 2008
ZEB2	All family members	Gregory *et al*, 2008a; Park *et al*, 2008; Korpal *et al*, 2008
TGF-β2	miR-141, miR-200c	Burk *et al*, 2008
ERBB receptor feedback inhibitor 1 (ERRFI1)	miR-200c	Adam *et al*, 2009
Friend of GATA 2 (FOG2)	All family members miR-8 (*Drosophila*)	Hyun *et al*, 2009
Polycomb ring finger oncogene (BMI1)	miR-200c	Shimono *et al*, 2009; Wellner *et al*, 2009
WAS protein family member 3 (WASF3, WAVE3)	miR-200b	Sossey-Alaoui *et al*, 2009
β-catenin (CTNNB1)	miR-200a	Xia *et al*, 2010
Class III beta-tubulin (TUBB3)	miR-200c	Cochrane *et al*, 2010
Phospholipase C gamma 1 (PLCG1)	miR-200b/c, miR-429	Uhlmann *et al*, 2010
FAS-associated phosphatase 1 (FAP1)	miR-200c	Schickel *et al*, 2010

miR, microRNA; ZEB, zinc-finger enhancer binding.

IPF



Tubb3-p63

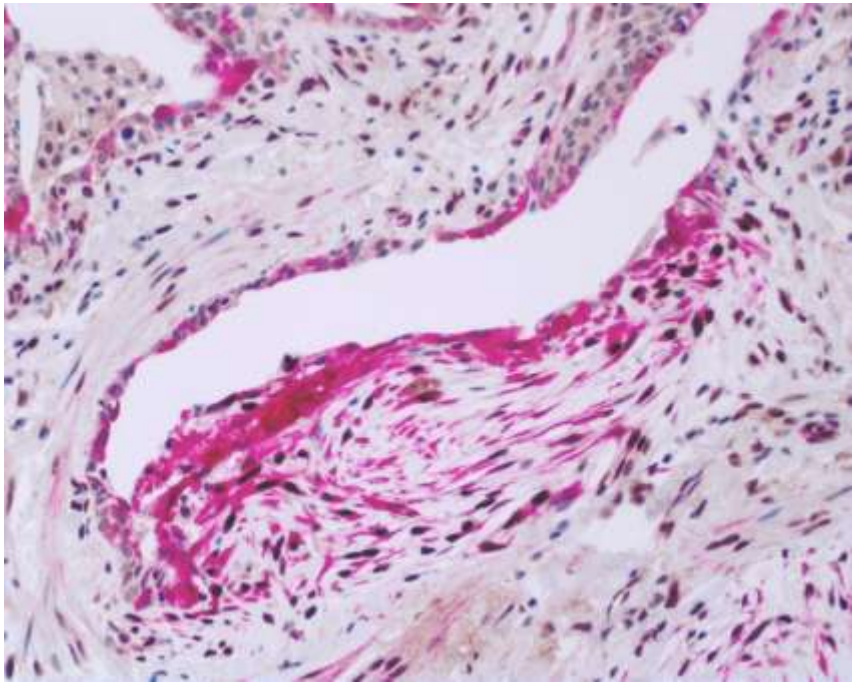


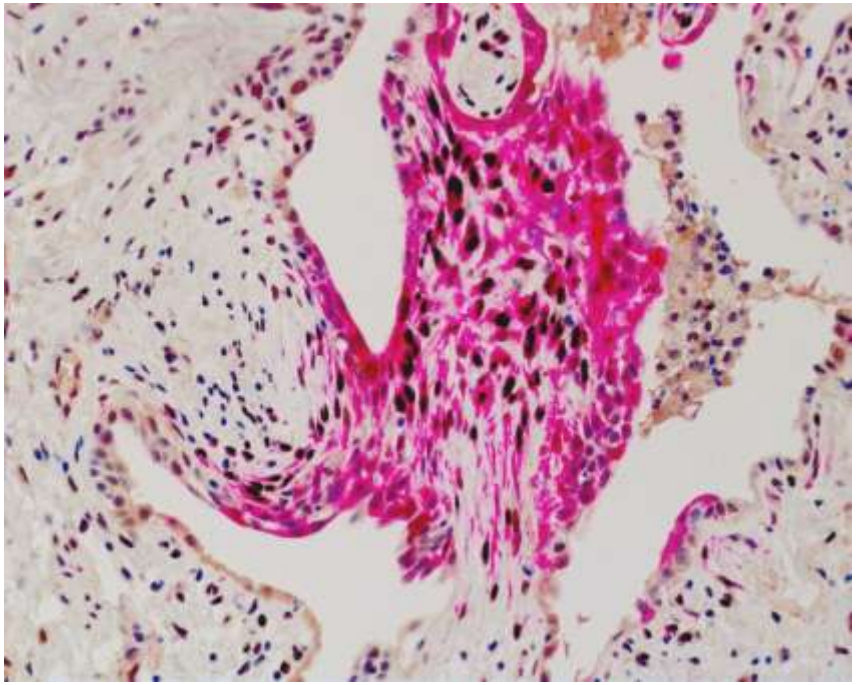
Tubb3 + twist

Chilosi et al, in preparation

IPF

Tubb3 + ZEB1





Chilosi et al, in preparation

Cell Cycle 9:5, 886-891; March 1, 2010; © 2010 Landes Bioscience

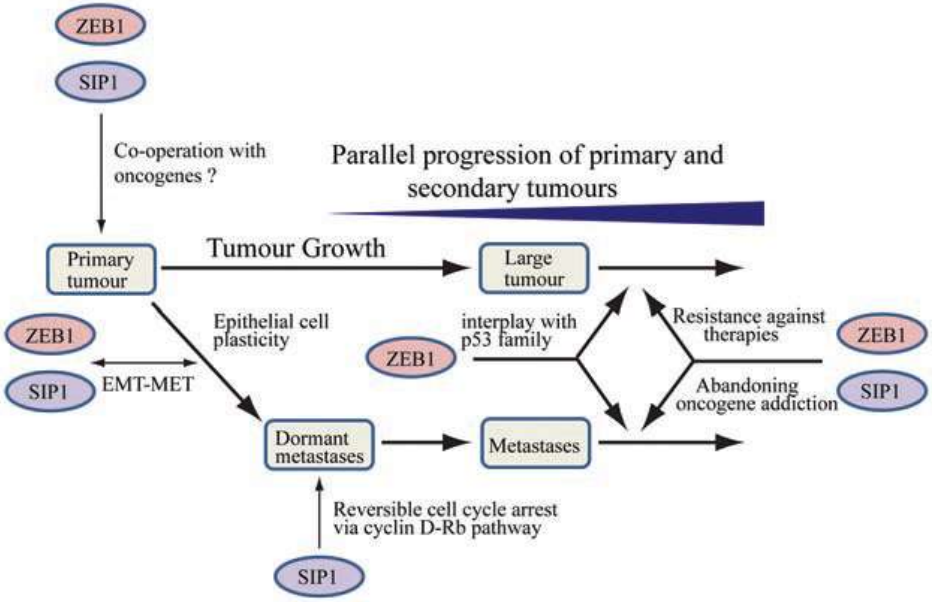
ZEB proteins link cell motility with cell cycle control and cell survival in cancer

Gareth Browne, A. Emre Sayan and Eugene Tulchinsky*

Department of Cancer Studies and Molecular Medicine; University of Leicester; Leicester, UK

Key words: epithelial mesenchymal transition, cell cycle, apoptosis, senescence, ZEB1, SIP1

Epithelial mesenchymal transitions (EMT), the generation of motile mesenchymal cells from epithelial sheets, are differentiation programs which take place at several critical steps of embryonic development and in metastatic cancer. Recent data have shown that the transcription factors which are master regulators of EMT also regulate cell cycle progression, apoptosis and senescence. In light of these new observations, the role of these factors in human cancer may be broader than previously anticipated. Here we review recent literature on non-EMT functions of EMT-controlling transcription factors. We will mainly focus on transcription factors belonging to the ZEB family, but some important results obtained by investigators studying other key EMT regulators, Snail and Twist are also discussed.



Respiratory Research

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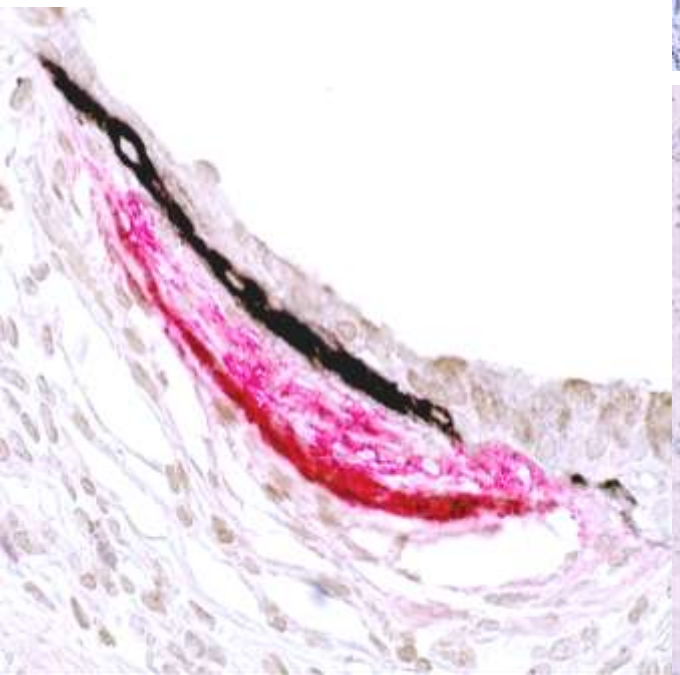
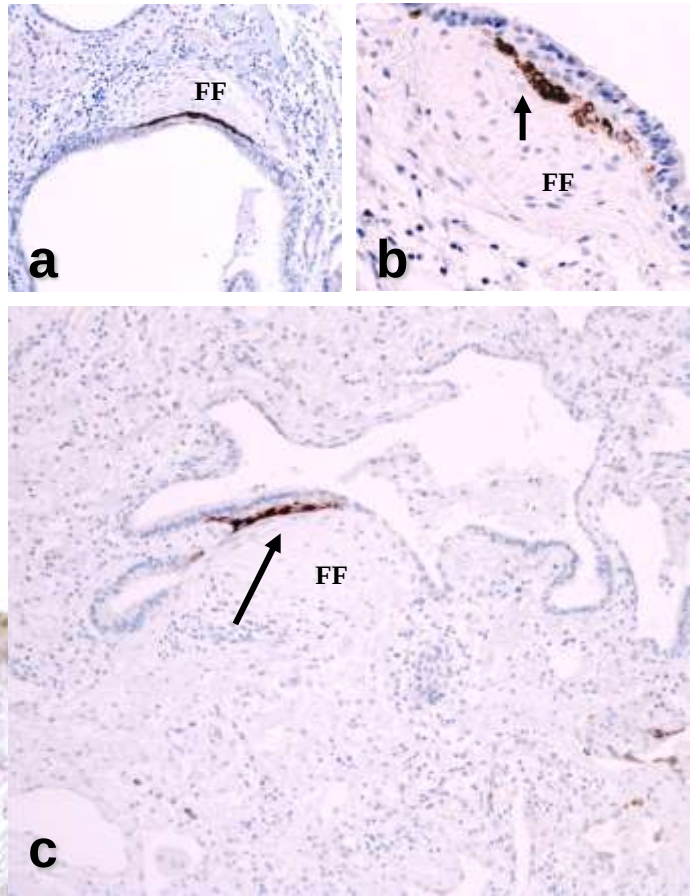
Migratory marker expression in fibroblast foci of idiopathic pulmonary fibrosis

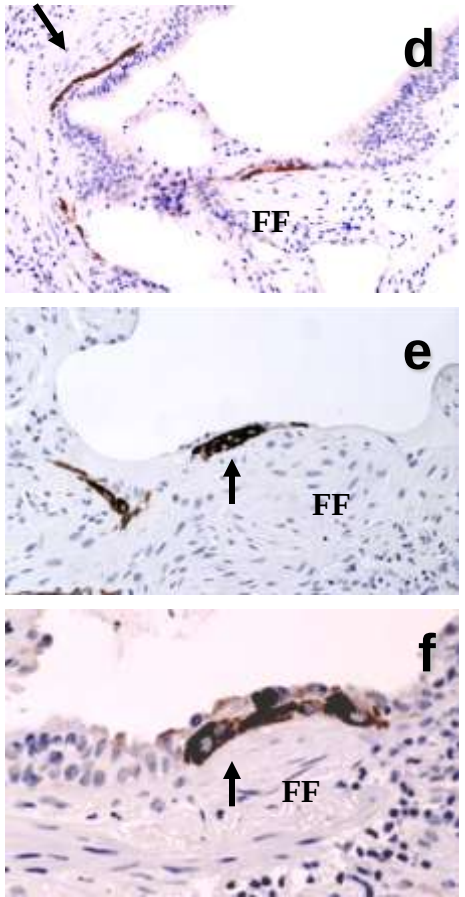
Marco Chilosi*[1], Alberto Zamò[1], Claudio Doglioni[2], Daniela Reghellin[1], Maurizio Lestani[1], Licia Montagna[1], Serena Pedron[1], Maria Grazia Ennas[3], Alessandra Cancellieri[4], Bruno Murer[5] and Venerino Poletti[6]

HSP27

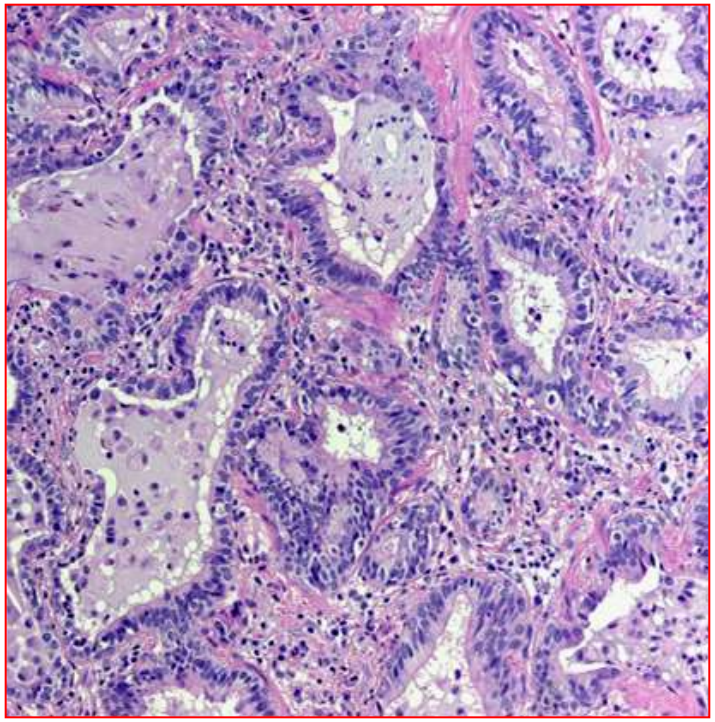
Laminin-5γ2

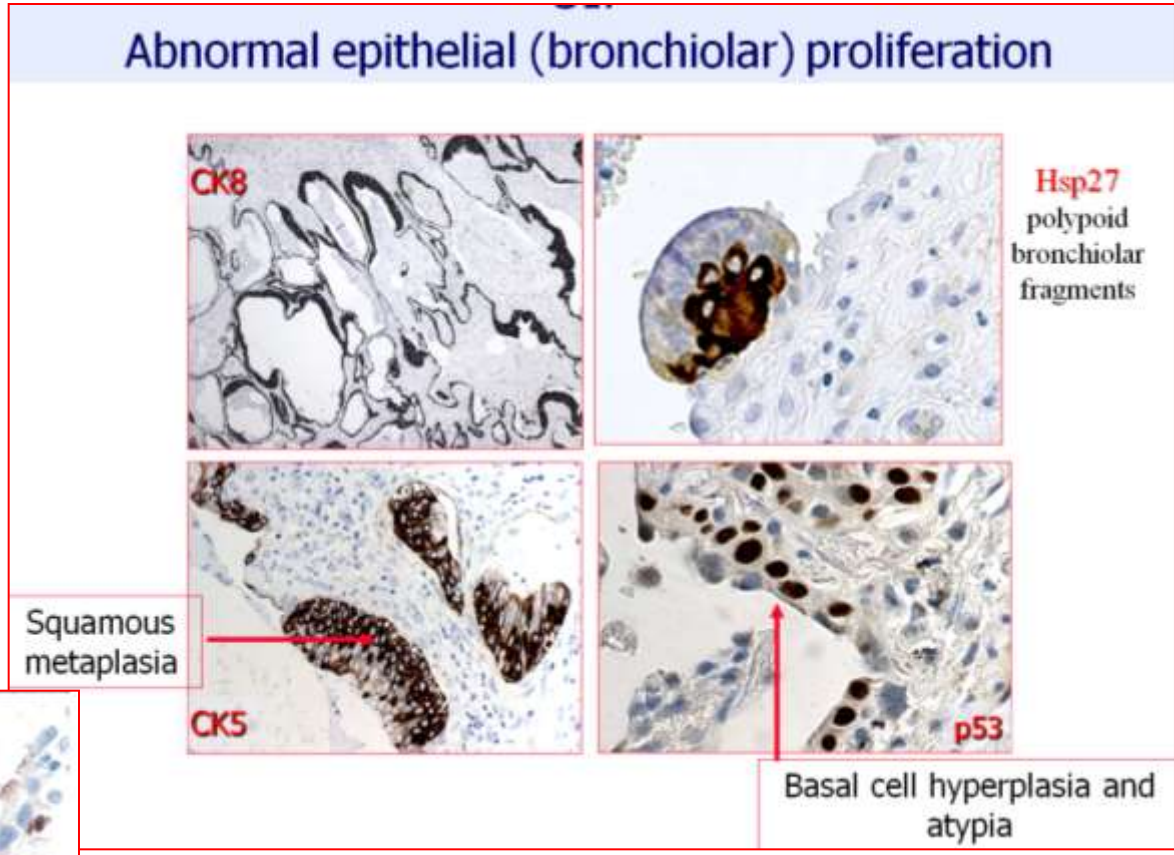


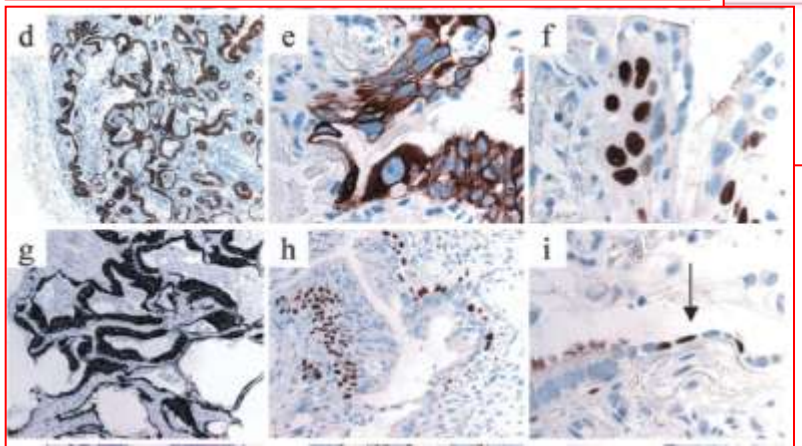




Lab Invest. 2002 Oct;82(10):1335-45.
Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63.
Chilosi M, Poletti V, Murer B, Lestani M, Cancellieri A, Montagna L, Piccoli P, Cangi G, Semenzato G, Doglioni C.







ΔN-p63

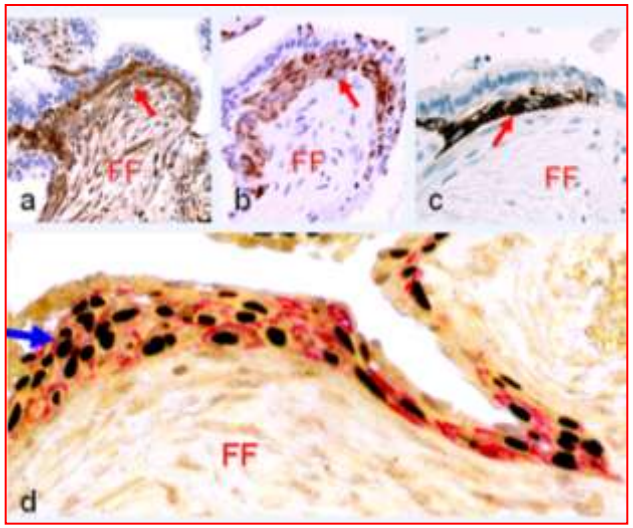
Bronchiolar dysplasia in IPF: molecular features

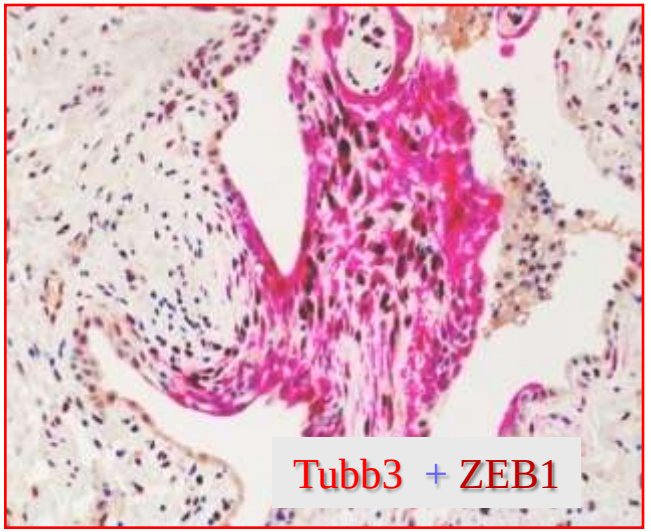
Hyper-expression

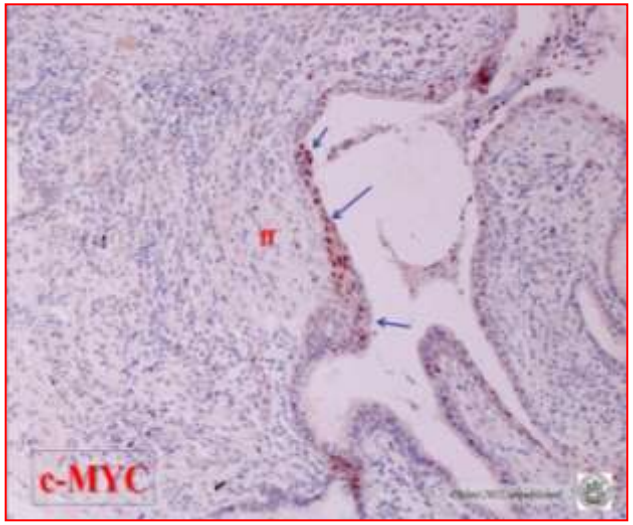
- N-beta-Catenin
- Laminin-5g2
- Hsp27
- Tubb3
- P63
- ZEB1
- MUC5B
- S100A4
- Fascin
- C-Myc
- MMP7
- K14

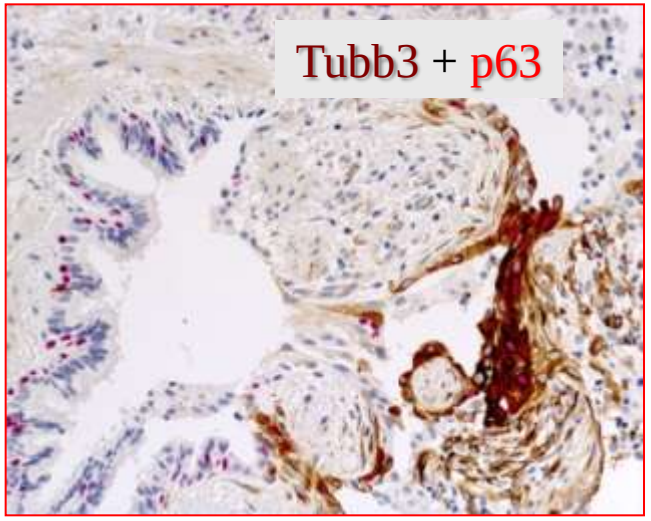
Under-expression

- SOX2
- MUC5AC







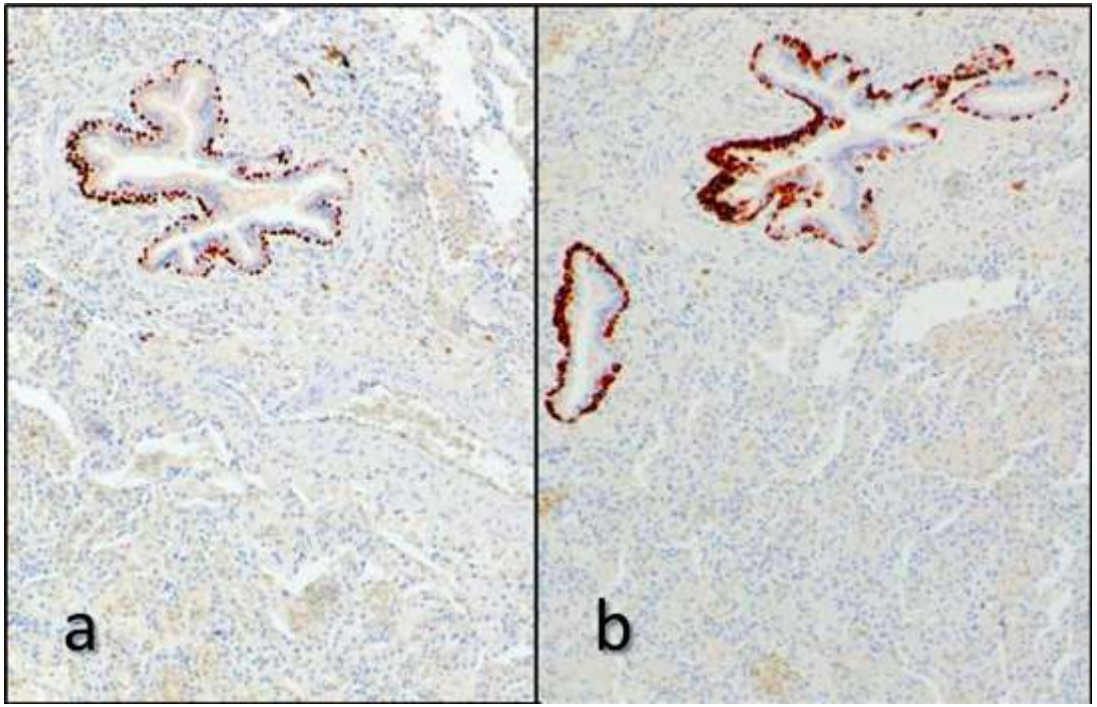


Chilosi et al, in preparation

Absence of bronchiolar proliferation

DAD/ARDS

CK5



Ficial M, Antonaglia C, Chilosi M, Santagiuliana M, Tahseen AO, Confalonieri D, Zandonà L, Bussani R, Confalonieri M. Keratin-14 expression in pneumocytes as a marker of lung regeneration/repair during diffuse alveolar damage. Am J Respir Crit Care Med. 2014 May 1;189(9):1142-5.

PLoS ONE 2013, 8(3): e58658.

OPEN ACCESS Freely available online

PLOS | ONE

The Idiopathic Pulmonary Fibrosis Honeycomb Cyst Contains A Mucocilary Pseudostratified Epithelium

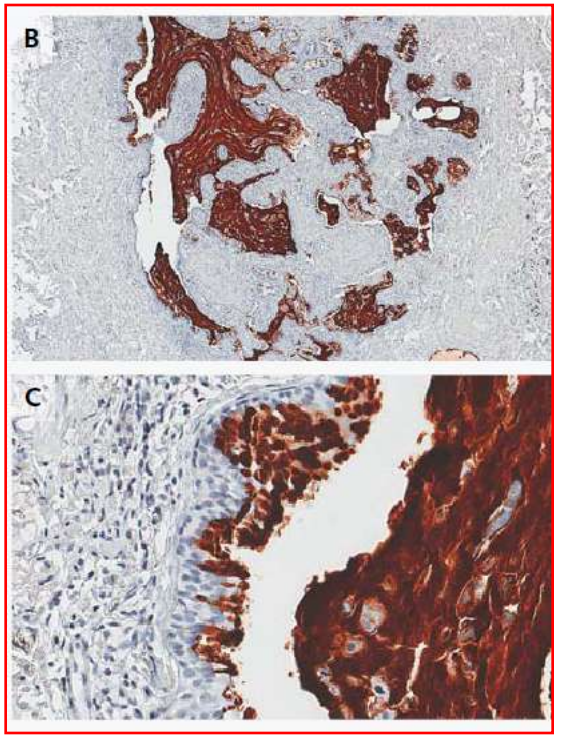
Max A. Seibold[1,2], Russell W. Smith[2], Cydney Urbanek[1], Steve D. Groshong[3], Gregory P. Cosgrove[3], Kevin K. Brown[3], Marvin I. Schwarz[3], David A. Schwartz[1,3☯], Susan D. Reynolds[2*☯]

1 Center for Genes, Environment and Health, National Jewish Health, Denver, Colorado, United States of America, **2** Department of Pediatrics, National Jewish Health, Denver, Colorado, United States of America, **3** Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, United States of America

The NEW ENGLAND JOURNAL of MEDICINE

Seibold MA, et al. N Engl J Med 2011;364:1503-12.

A Common *MUC5B* Promoter Polymorphism and Pulmonary Fibrosis

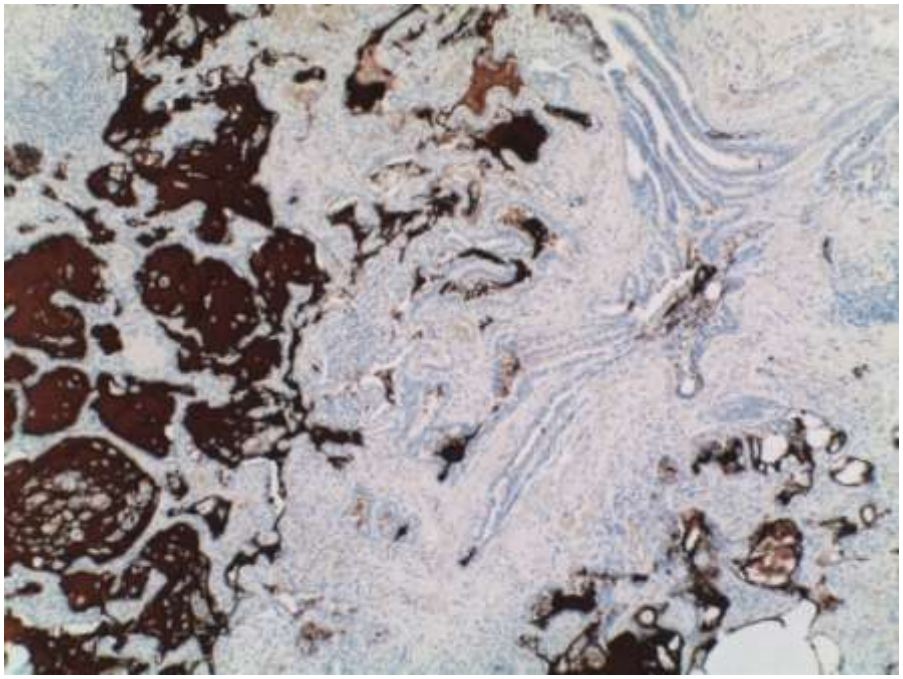


Ectopic respiratory epithelial cell differentiation in bronchiolised distal airspaces in idiopathic pulmonary fibrosis

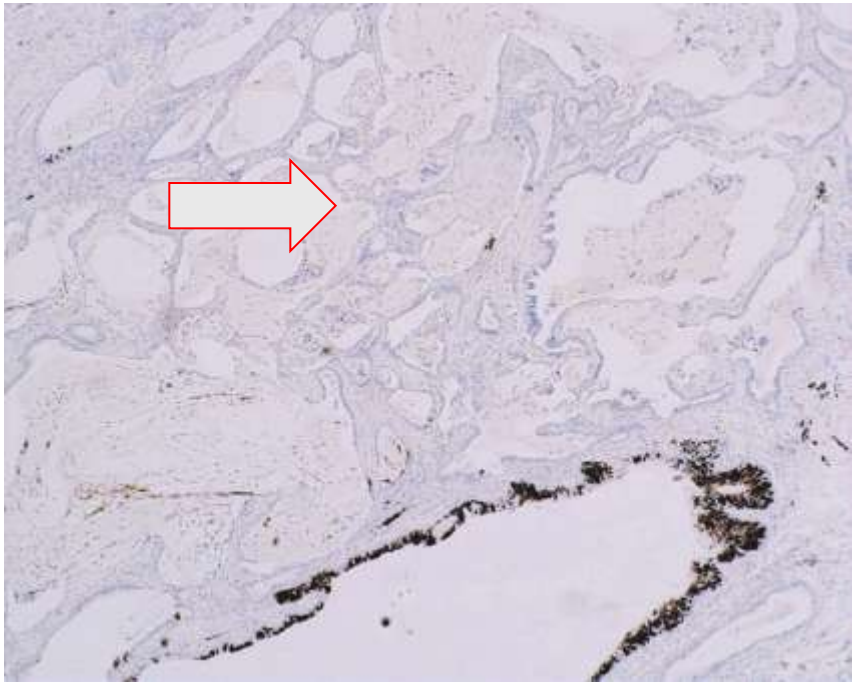
Thorax. 2011 Aug;66(8):651-7.

Laurent Plantier,[1] Bruno Crestani,[2,3] Susan E Wert,[1] Monique Dehoux,[3,4] Barbara Zweytick,[5] Andreas Guenther,[6,7] Jeffrey A Whitsett[1]

IPF: abnormal mucin5 expression in Honeycomb cysts

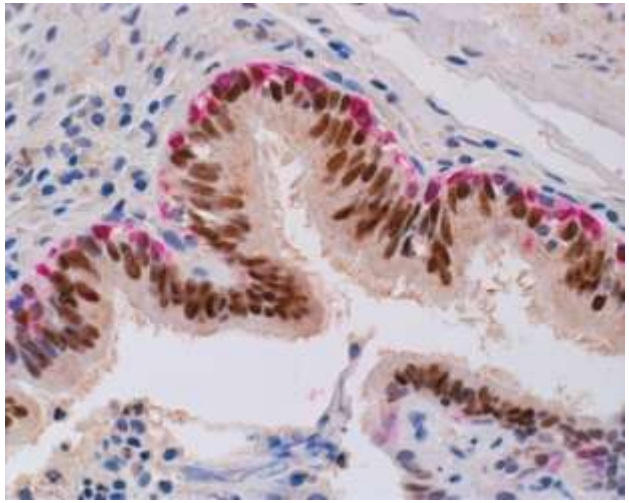


MUC5B

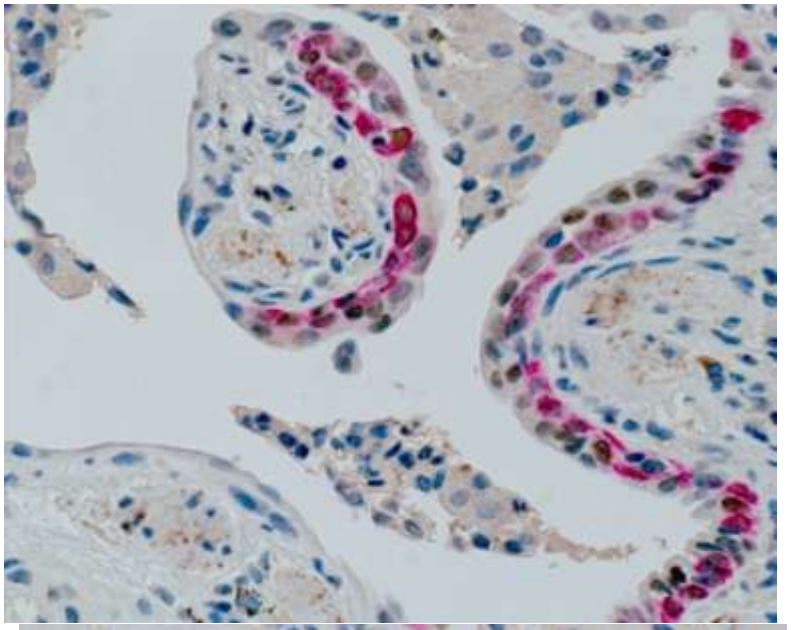


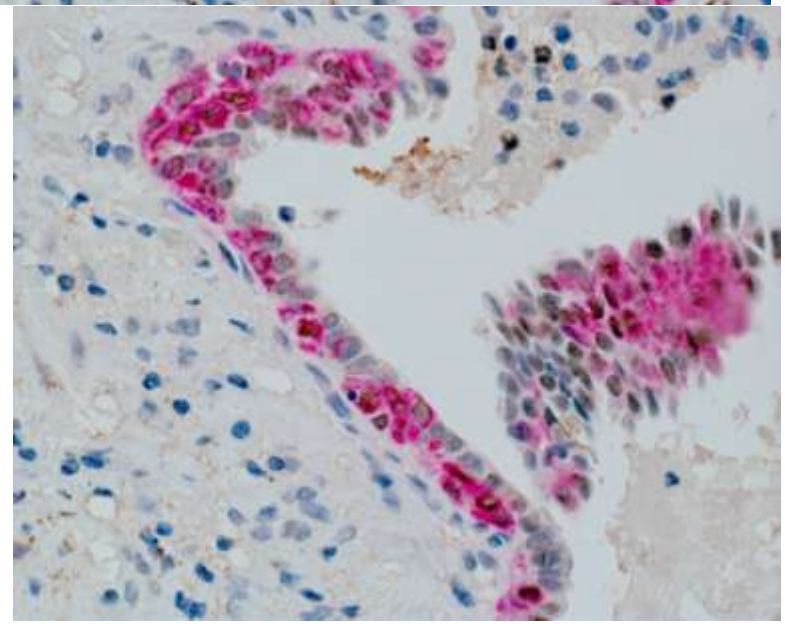
MUC5AC

CK5/sox2



Normal bronchiole





Sox2 is lost in micro-honeycombing

Chilosi et al., in preparation

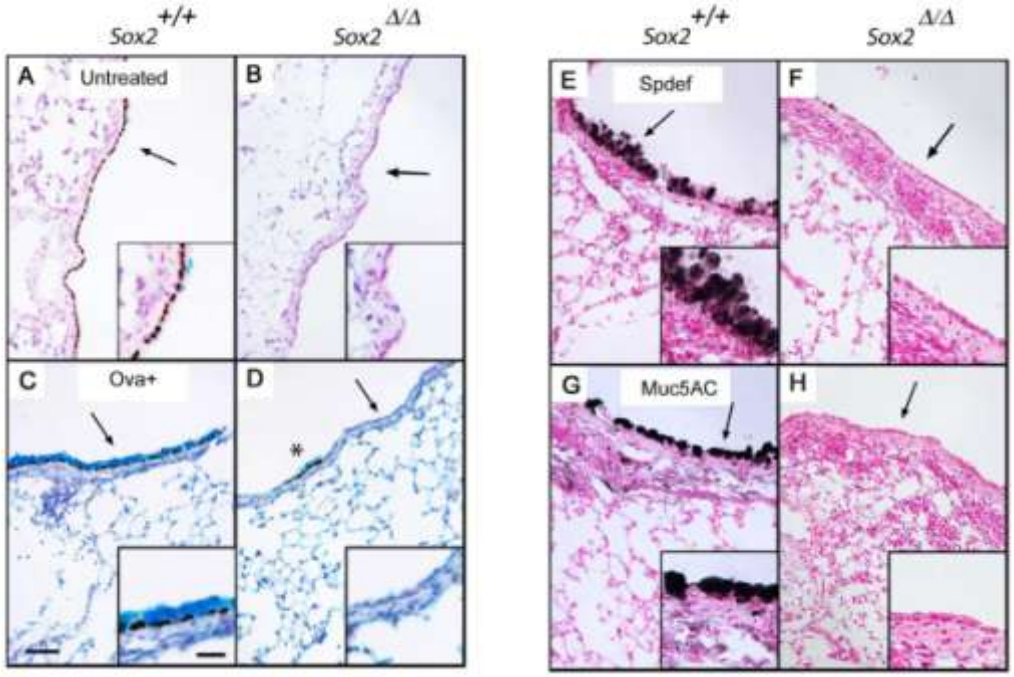
OPEN ACCESS Freely available online

PLoS one

Sox2 Is Required for Maintenance and Differentiation of Bronchiolar Clara, Ciliated, and Goblet Cells

David H. Tompkins, Valérie Besnard, Alexander W. Lange, Susan E. Wert, Angela R. Keiser, April N. Smith, Richard Lang, Jeffrey A. Whitsett*

Division of Pulmonary Biology in the Perinatal Institute and Division of Pediatric Ophthalmology, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America



β-Catenin–SOX2 signaling regulates the fate of developing airway epithelium

Shuichi Hashimoto[1,2], Huaiyong Chen[1,2], Jianwen Que[2], Brian L. Brockway[1,2], Jeffrey A. Drake[1,2], Joshua C. Snyder[1,2], Scott H. Randell[3] and Barry R. Stripp[1,2,*]

[1]Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Duke University Medical Center, 106 Research Drive, 2075 MSRBII, DUMC Box 103000, Durham, NC, 27710, USA
[2]Department of Cell Biology, Duke University Medical Center, Box 3709, Durham, NC, 27710, USA
[3]Departments of Cell and Molecular Physiology and Medicine, The University of North Carolina at Chapel Hill, 111 Mason Farm Road, 5200 Medical Biomolecular Research Building, CB 7545 Chapel Hill, NC, 27599-7545, USA

*Author for correspondence (barry.stripp@duke.edu)

Accepted 11 September 2011
Journal of Cell Science 125, 932–942

doi: 10.1242/jcs.092734

Summary

Wnt–β-catenin signaling regulates cell fate during organ development and postnatal tissue maintenance, but its contribution to specification of distinct lung epithelial lineages is still unclear. To address this question, we used a Cre recombinase (Cre)-LoxP approach to activate canonical Wnt signaling ectopically in developing lung endoderm. We found that persistent activation of canonical Wnt signaling within distal lung endoderm was permissive for normal development of alveolar epithelium, yet led to the loss of developing bronchiolar epithelium and ectasis of distal conducting airways. Activation of canonical Wnt led to ectopic expression of a lymphoid-enhancing factor and a T-cell factor (LEF and TCF, respectively) and absence of SRY (sex-determining region Y)-box 2 (SOX2) and tumor protein p63 (p63) expression in proximal derivatives. Conditional loss of SOX2 in airways phenocopied epithelial differentiation defects observed with ectopic activation of canonical Wnt. Our data suggest that Wnt negatively regulates a SOX2-dependent signaling program required for developmental progression of the bronchiolar lineage.

Key words: Wnt, SOX2, Lung development, Endoderm, Bronchiolar epithelium

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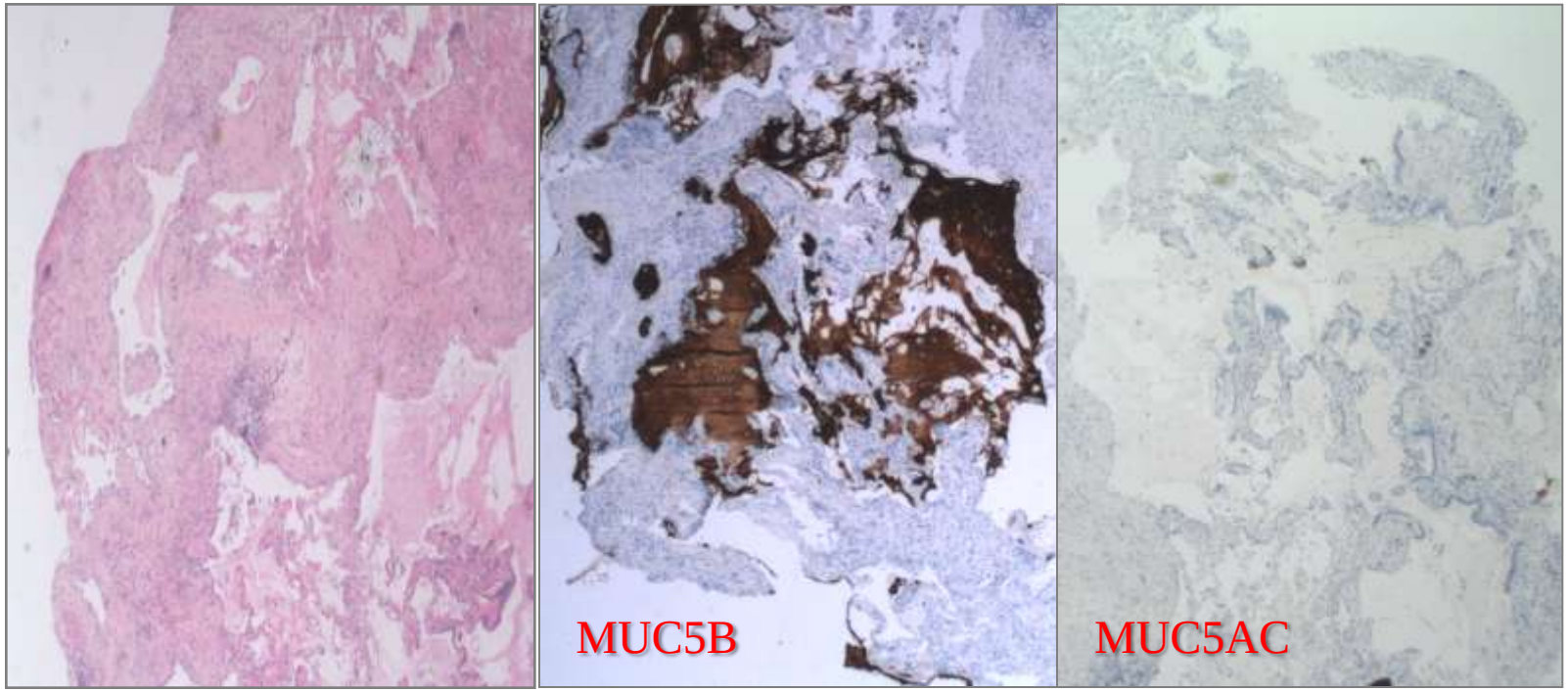
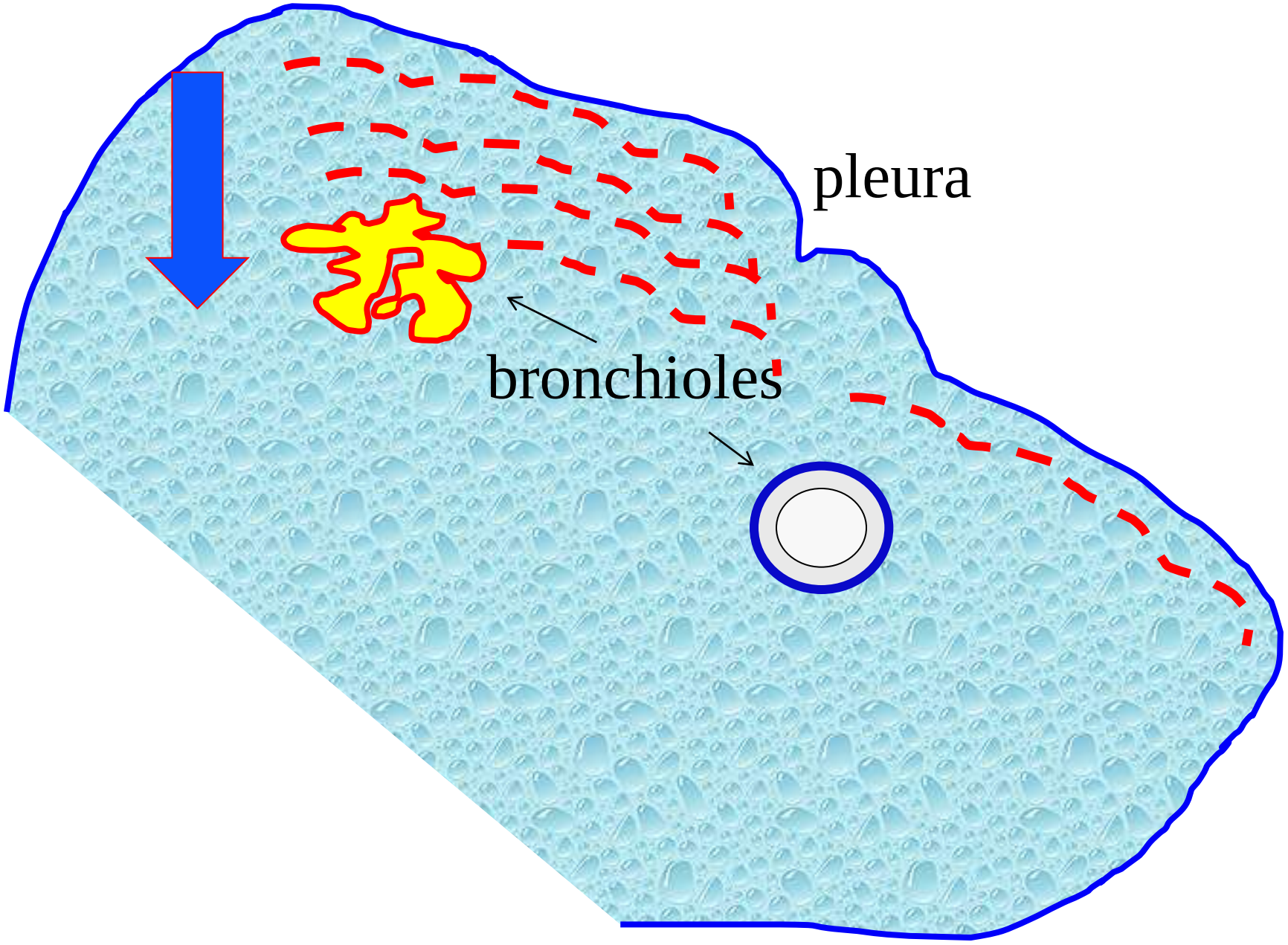
PLOS ONE

Transbronchial Lung Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Diseases

Gian Luca Casoni[1☯], Sara Tomassetti[1☯], Alberto Cavazza[2], Thomas V. Colby[3], Alessandra Dubini[4], Jay H. Ryu[5], Elisa Carretta[6], Paola Tantalocco[1], Sara Piciucchi[7], Claudia Ravaglia[1], Christian Gurioli[1], Micaela Romagnoli[1], Carlo Gurioli[1], Marco Chilosi[8], Venerino Poletti[1]*

1 Department of Diseases of the Thorax, G.B Morgagni Hospital, Forlì, Italy, **2** Department of Pathology, S. Maria Nuova Hospital-I.R.C.C.S, Reggio Emilia, Italy, **3** Department of Pathology, Mayo Clinic, Scottsdale, Arizona, United States of America, **4** Department of Pathology, G.B Morgagni Hospital, Forlì, Italy, **5** Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, United States of America, **6** Biostatistics and Clinical Trials Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola Forlì-Cesena, Italy, **7** Department of Radiology, G.B Morgagni Hospital, Forlì, Italy, **8** Department of Pathology, Verona University, Verona, Italy




pleura
bronchioles

Renewal strategies in bronchiolar and alveolar epithelia are different

Rigged game

TAp63

telomerase

C-Myc

AECII

β-catenin

Surfactant SPA

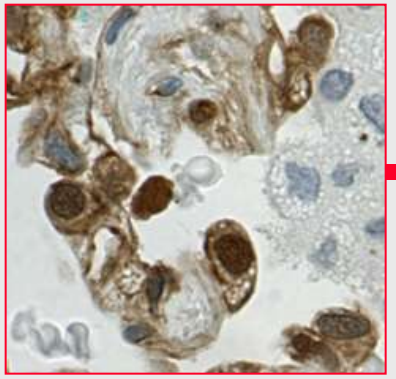
AEC-I

ΔN-p63

CK5

TA-p63
P53
P21waf1
p16

Alveolar pneumocytes



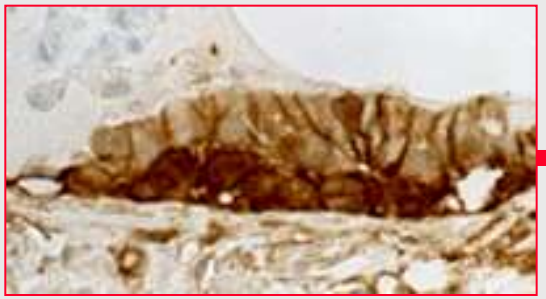
apoptosis

β-catenin
as transcription factor

cyclin-D1

c-myc

Bronchiolar basal cells

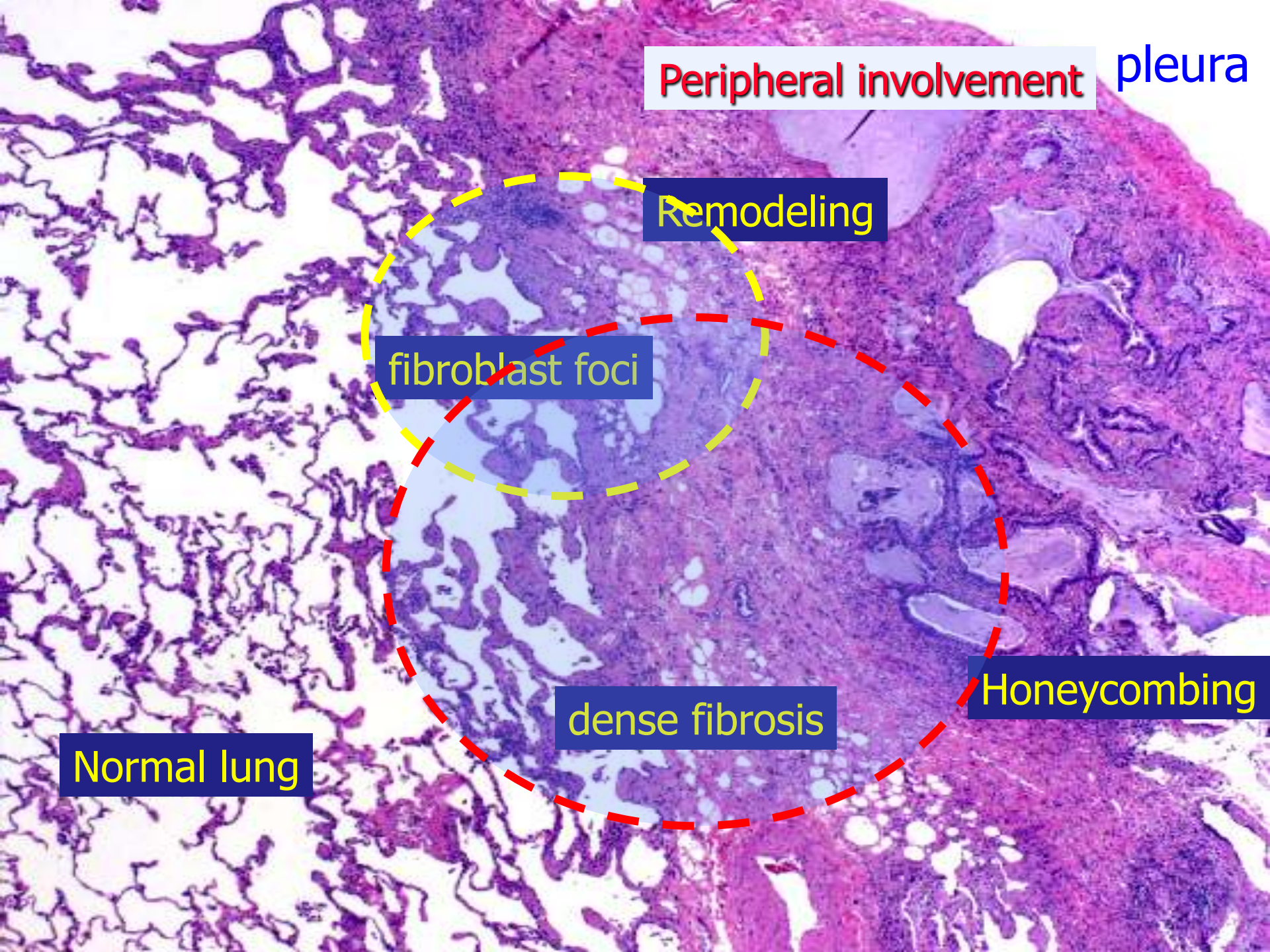


Proliferation

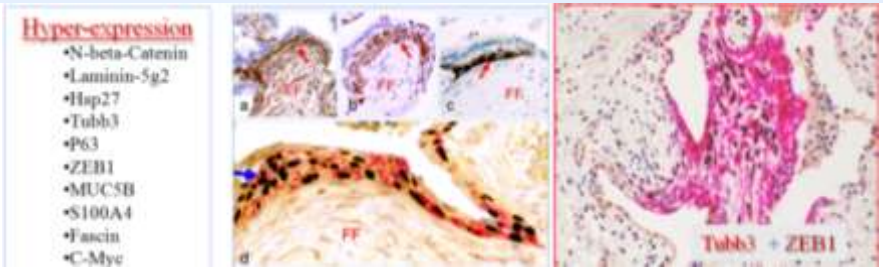
ΔN-p63
P53
p21waf1

MMP7
LAM5γ2
HSP27

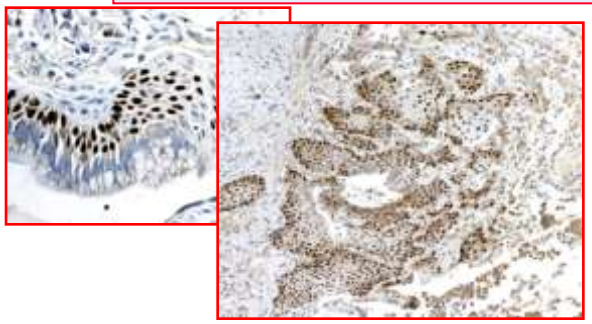
Cell-motility

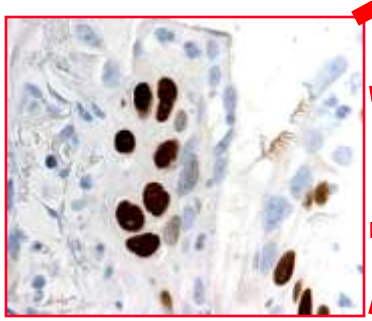

Peripheral involvement
pleura
Remodeling
fibroblast foci
dense fibrosis
Honeycombing
Normal lung

From “bronchiolar Dysplasia to carcinoma in IPF/UIP



Squamous carcinoma





adenocarcinoma

Goblet-metaplasia

m-BAC

Abnormal stem (basal) cells

WNT-abnormal activation

Intestinal-type adenocarcinoma

from **Erinyes** (Ἐρῑνύες) “furiae” to
Eumenides (Εὐμενίδες) "Kindly Ones")

PNAS

Inhibition of Wnt/β-catenin/CREB binding protein (CBP) signaling reverses pulmonary fibrosis

William R. Henderson, Jr.[a,1], Emil Y. Chi[b], Xin Ye[a], Cu Nguyen[c], Ying-tzang Tien[b], Beiyun Zhou[d], Zea Borok[d,e], Darryl A. Knight[f], and Michael Kahn[c,e,1]

[a]Center for Allergy and Inflammation and Department of Medicine, University of Washington, Seattle, WA 98109; [b]Department of Pathology, University of Washington, Seattle, WA 98195; [c]Center for Stem Cell and Regenerative Medicine, [d]Will Rogers Institute Pulmonary Research Center and Department of Medicine, [e]Department of Biochemistry and Molecular Biology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033; and [f]Department of Pharmacology and Therapeutics and James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, University of British

2014

Sci Transl Med. 2014 Apr 9;6(231):231ra47. doi: 10.1126/scitranslmed.3008182.

Reversal of persistent fibrosis in aging by targeting Nox4-Nrf2 redox imbalance.

Hecker L[1], Logsdon NJ, Kurundkar D, Kurundkar A, Bernard K, Hock T, Meldrum E, Sanders YY, Thannickal VJ.

Am J Physiol Cell Physiol. 2014 Jun 4. pii: ajpcell.00163.2014. [Epub ahead of print]

A two-pronged weapon in the fight against fibrosis. Focus on "Inhibition of Wnt/β-Catenin Signaling Repairs Bleomycin-induced Lung Injury"

Ostrom RS

J Cell Physiol. 2014 Feb;229(2):213-24. doi: 10.1002/jcp.24436.

Inhibition of Wnt/β-catenin signaling promotes engraftment of mesenchymal stem cells to repair lung injury.

Sun Z[1], Gong X, Zhu H, Wang C, Xu X, Cui D, Qian W, Han X.

Journal of Pathology
J Pathol 2014; **232**: 391–404
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4316

ORIGINAL PAPER

EMILIN2 down-modulates the Wnt signalling pathway and suppresses breast cancer cell growth and migration

Stefano Marastoni,[1] Eva Andreuzzi,[1] Alice Paulitti,[1] Roberta Colladel,[1] Rosanna Pellicani,[1] Federico Todaro,[1] Alvise Schiavinato,[2] Paolo Bonaldo,[2] Alfonso Colombatti[1,3] and Maurizio Mongiat[1]*

PULMONARY PERSPECTIVE

Revealing the Pathogenic and Aging-related Mechanisms of the Enigmatic Idiopathic Pulmonary Fibrosis

An Integral Model

Moisés Selman[1] and Annie Pardo[2]

[1]Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas," México DF, Mexico; and [2]Facultad de Ciencias, Universidad Nacional Autónoma de México, México DF, Mexico

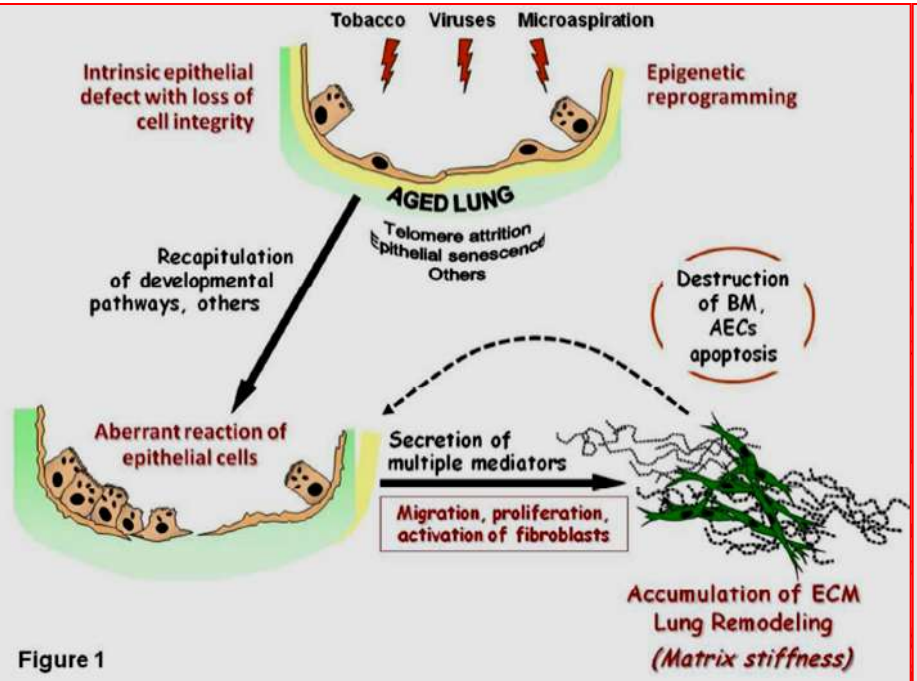
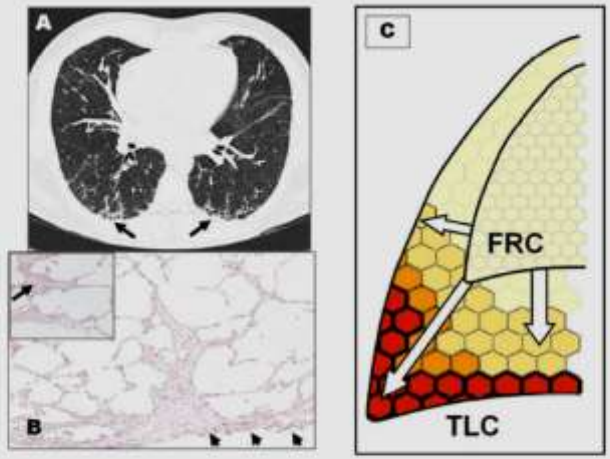
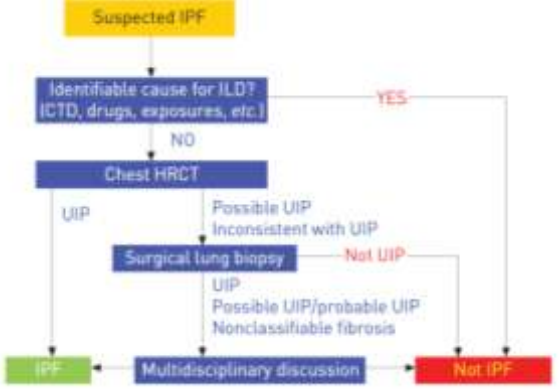


Figure 1



Characteristic initial chest tomography (A) and morphologic (B) alterations in idiopathic pulmonary fibrosis. The arrows indicate the typical bibasal, subpleural reticular and cystic images (A), and the subpleural fibrotic lesion in otherwise almost normal lung (B). The arrow in the inset show a subepithelial fibroblastic focus, and hyperplastic alveolar epithelial cells. Panel C shows the hypothetical distribution of maximal mechanical stress obtained by a simplified mathematical model (29). In functional residual capacity (FRC) the alveoli are "semi-open". In inspiration the air is heterogeneously distributed within the lung parenchyma with the maximal mechanical stress in the peripheral (subpleural areas) of the lung that represent sites of early lesions.

254x190mm (96 x 96 DPI)



Diagnosis and management of idiopathic pulmonary fibrosis: French practical guidelines

Vincent Cottin, Bruno Crestani, Dominique Valeyre, Benoit Wallaert, Jacques Cadranel, Jean-Charles Dalphin, Philippe Delaval, Dominique Israel-Biet, Romain Kessler, Martine Reynaud-Gaubert, Bernard Aguilaniu, Benoit Bouquillon, Philippe Carré, Claire Danel, Jean-Baptiste Faivre, Gilbert Ferretti, Nicolas Just, Serge Kouzan, François Lebargy, Sylvain Marchand-Adam, Bruno Philippe, Grégoire Prévot, Bruno Stach, Françoise Thivolet-Béjui, Jean-François Cordier and the French National Reference Centre and the Network of Competence Centres for Rare Lung Diseases

Question 4: When should genetic testing be performed in patients suspected of having IPF?

Eur Respir Rev. 2014 Jun;23(132):193-214

Recommendation

If a diagnosis of IPF is suspected, it is recommended that tests are systematically performed during the medical interview to identify the presence of other causes of ILD within the family, and to search for clinical and biological signs suggesting a genetic cause (hepatic, cutaneous, mucosal and haematological abnormalities).

It is proposed that patients presenting with IPF in a familial context be referred to an outpatient clinic specialising in genetics to establish a pedigree and propose genetic molecular analysis primarily targeting, with the currently available of knowledge, the telomerase complex genes and the surfactant protein-C genes.

Comment

Familial forms of IPF affecting <5% of patients have been reported [20–23]. The probability of a genetic cause seems to be higher in younger individuals (in particular those aged <50 years).

Most frequently, the mode of genetic transmission of IPF in those familial cases is an autosomal dominant pattern of inheritance with variable penetrance [21, 22, 24–26]. A congenital form of dyskeratosis, characterised by a mutation of the telomerase complex genes (*TERT* and *TERC*), may be suggested by clinical and biological abnormalities, including macrocytosis, refractory anaemia due to erythroblastopenia, cryptogenic hepatic cirrhosis, abnormal cutaneous pigmentation, mucosal abnormalities such as leukoplakia of the tongue margin, or leukotrichia (premature greying of hair) [27].